

Fig. 1 Cleavage and Polyadenylation Process For The
 SV40 early Poly(A) site

A. CTTATCGATACCGTCGAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCAT
 CACAAATTTACAAATAAAGCATTCTAGTTGTGGTTTGTCCAACTCATCA
 ATGTATCTTATCATGTC (Seq ID NO:1) Cleavage site

B. 

C.  (Seq ID NO:18)

+ Upstream and downstream
 cleavage-polyadenylation elements

1001969.03303

(Seq ID NO:2)

Fig 2 E1A transcription control region



A. Nucleotides 1-1802 containing ITR, polyA, E2F-1 promoter, E1a and a portion of the E1b gene (Seq ID NO:3)

	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2
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961 CTGGCTTTCCACCCAGTGACGACGAGGATGAAGAGGGTGAGGAGTTTGTGTAGATTATG
-----E1a gene-----
1021 TGGAGCACCCCGGGCACGTTGCAGGTCCTGTGCATTATCACCGGAGGAATACGGGGGACC
-----E1a gene-----
1081 CAGATATTATGTGTTTCGCTTTGCTATATGAGGACCTGTGGCATGTTTGTCTACAGTAAGT
-----E1a gene-----
1141 GAAAATTATGGGCAGTGGGTGATAGAGTGGTGGGTTTGGTGTGGTAATTTTTTTTTTAAAT
-----E1a gene-----
1201 TTTTACAGTTTTTGTGGTTTAAAGAATTTTGTATTGTGATTTTTTTTAAAAGGTCTGTGTC
-----E1a gene-----
1261 TGAACCTGAGCCTGAGCCCGAGCCAGAACCGGAGCCTGCAAGACCTACCCGCCGTCTCTAA
-----E1a gene-----
1321 AATGGCGCCTGCTATCCTGAGACGCCCCGACATCACCTGTGTCTAGAGAATGCAATAGTAG
-----E1a gene-----
1381 TACGGATAGCTGTGACTCCGGTCCTTCTAACACACCTCCTGAGATACACCCGGTGGTCCC
-----E1a gene-----
1441 GCTGTGCCCCATTAAACCAGTTGCCGTGAGAGTTGGTGGGCGTCGCCAGGCTGTGGAATG
-----E1a gene-----
1501 TATCGAGGACTTGCTTAACGAGCCTGGGCAACCTTTGGACTTGAGCTGTAAACGCCCCAG
-----E1a gene-----
1561 GCCATAAGGTGTAAACCTGTGATTGCGTGTGTGGTTAACGCCTTTGTTTGCTGAATGAGT
-----E1a gene-----
1621 TGATGTAAGTTTAATAAAGGGTGAGATAATGTTTAACTTGCATGGCGTGTTAAATGGGGC
-----+-----
1681 GGGGCTTAAAGGGTATATAATGCGCCGTGGGCTAATCTTGGTTACATCTGACCTCATGGA
-----E1b gene-----
1741 GGCTTGGGAGTGTGTTGGAAGATTTTTCTGCTGTGCGTAACTTGCTGGAACAGAGCTCTAA
-----E1b gene-----
1801 CA
--

B. Nucleotides 33881-34412 containing packaging signal and ITR (Seq ID NO:4)

33881 AACCTACGCCAGAAACGAAAGCCAAAAAACCACAACTTCCTCAAATCGTCACTTCCGT
33941 TTTCCACGTTACGTCACTTCCCATTTTAATTAAGAATTCTACAATTCCCAACACATACA

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34001 AGTTACTCCGCCCTAAAACCCTGGGCGAGTCTCCACGTAAACGGTCAAAGTCCCCGCGGC
+--packaging signal-----

34061 CCTAGACAAATATTACGCGCTATGAGTAACACAAAATTATTCAGATTTCACTTCCTCTTA
-----packaging signal-----

34121 TTCAGTTTTCCCGCGAAAATGGCCAAATCTTACTCGGTTACGCCCAAATTTACTACAACA
-----packaging signal-----

34181 TCCGCCTAAAACCGCGCGAAAATTGTCACTTCCTGTGTACACCGGCGCACACCAAAAACG
-----+

34241 TCACTTTTGCCACATCCGTCGCTTACATGTGTTCCGCCACACTTGCAACATCACACTTCC

34301 GCCACACTACTACGTACCCGCCCCGTTCCCACGCCCCGCGCCACGTCACAAACTCCACC
+-----ITR-----

34361 CCCTCATTATCATATTGGCTTCAATCCAAAATAAGGTATATTATTGATGATG
-----ITR-----+

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Figure 4. Sequence of Ar6F from left end of viral DNA (Seq ID NO:5)

1 CATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAGGGGGTGGAGT
+-----ITR-----

61 TTGTGACGTGGCGCGGGGCGTGGGAACGGGGCGGGTGACGTAGGGCGCGCCGCTAGCGAT
-----ITR-----++-----MCS-----

121 ATCGGATCCCGGTCGACTGAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGA
-----+-----E1a-----

181 AGAAATGGCCGCCAGTCTTTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCC
-----E1a-----

241 ACCTCCTAGCCATTTTGAACCACCTACCCTTCACGAAGTGTATGATTTAGACGTGACGGC
-----E1a-----

301 CCCCAGAGATCCCAACGAGGAGGCGGTTTTCGAGATTTTCCCGACTCTGTAATGTTGGC
-----E1a-----

361 GGTGCAGGAAGGGATTGACTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCC
-----E1a-----

421 TCACCTTTCCCGGCAGCCCGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCC
-----E1a-----

481 AAACCTTGTACCGGAGGTGATCGATCTTACCTGCCACGAGGCTGGCTTCCACCCAGTGA
-----E1a-----

541 CGACGAGGATGAAGAGGGTGAGGAGTTTGTGTTAGATTATGTGGAGCACCCGGGCACGG
-----E1a-----

601 TTGCAGGTCTTGTTCATTATCACCGGAGGAATACGGGGGACCCAGATATTATGTGTTTCGCT
-----E1a-----

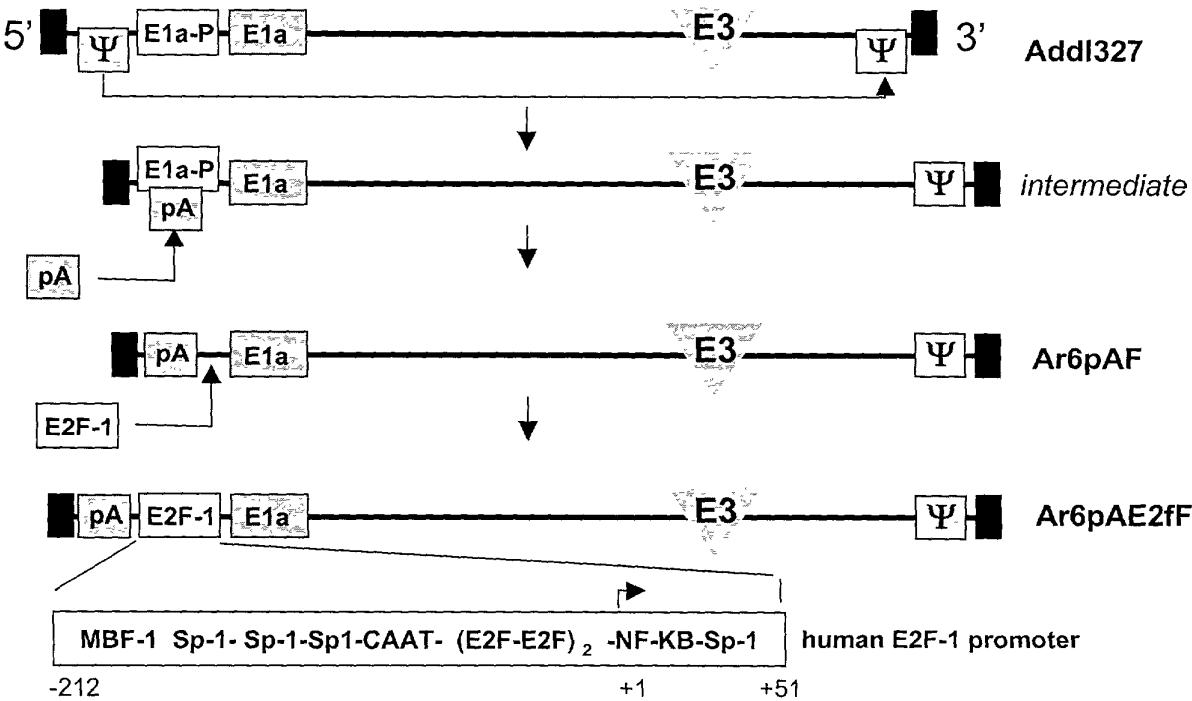
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Figure 5. Sequence of Ar6pAF from left end of viral DNA (Seq ID NO:6)

```
1  CATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAGGGGGTGGAGT
+-----IIR-----
61  TTGTGACGTGGCGCGGGCGTGGGAACGGGGCGGGTGACGTAGGGCGCGATCAAGCTTAT
-----IIR-----+
121  CGATACCGTCGAAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCATC
-----polyA-----
181  ACAAATTTACAAAATAAAGCATTTTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAAACTC
-----polyA-----
241  ATCAATGTATCTTATCATGTCTGGATCCGCGCCGCTAGCGATATCGGATCCCGGTCGACT
-----+
301  GAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGAAGAAATGGCCGCCAGTCT
-----E1a-----
361  TTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCCACCTCCTAGCCATTTTGA
-----E1a-----
421  ACCACCTACCCTTCACGAACTGTATGATTTAGACGTGACGGCCCCCGAAGATCCCAACGA
-----E1a-----
481  GGAGGCGGTTTCGCAGATTTTCCCGACTCTGTAATGTTGGCGGTGCAGGAAGGGATTGA
-----E1a-----
541  CTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGAGCCGCCTCACCTTTCCCGGCAGCC
-----E1a-----
601  CGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCCAAACCTTGTACCGGAGGT
-----E1a-----
```

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Figure 6. Schematic diagram of Ar6pAF and Ar6pAE2fF vectors



9/73

Fig. 7 Body weight change

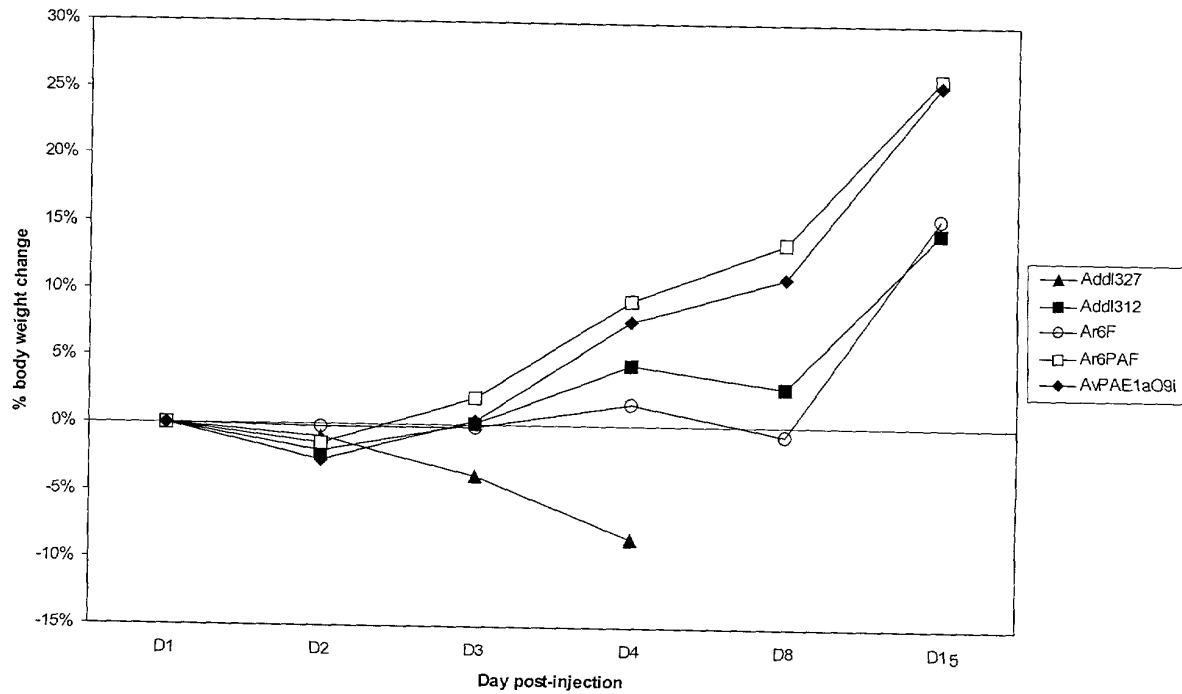
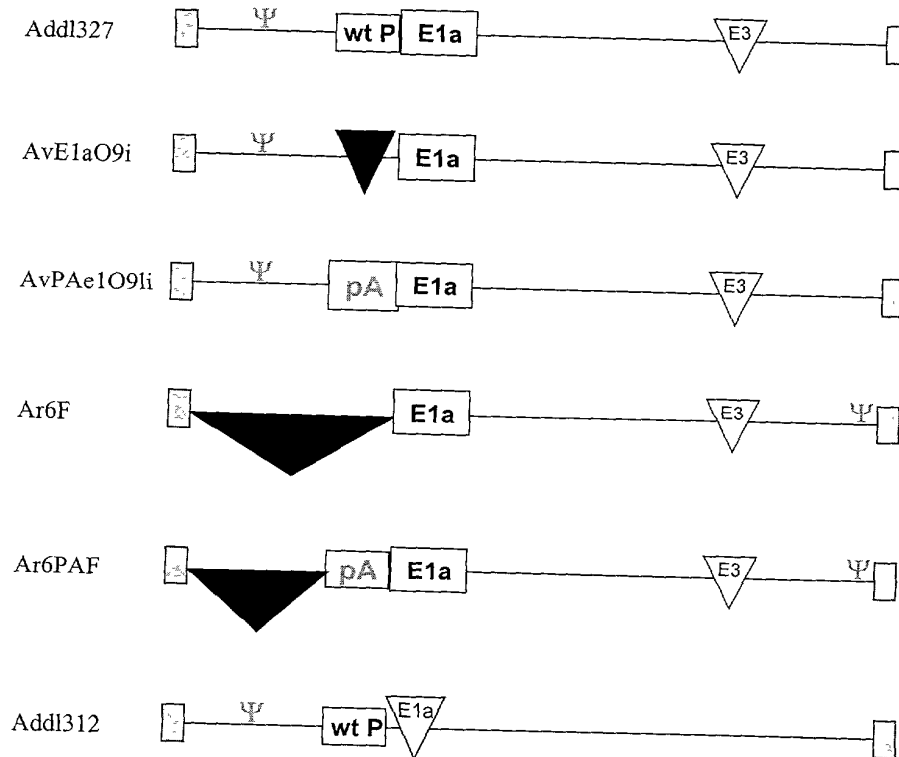


Fig. 8 Minimizing nonspecific transactivation of E1a gene

Backbones generated:



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11/73

Figure 9. Mean H460 tumor volume

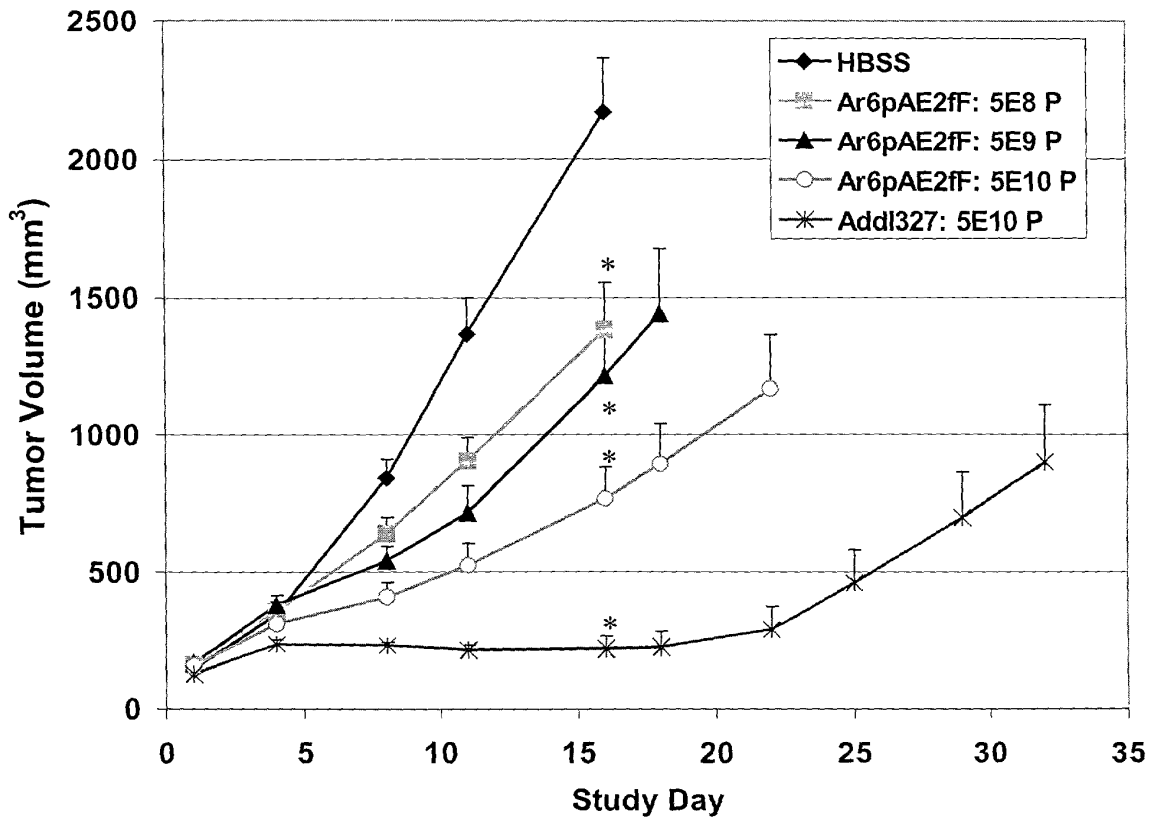
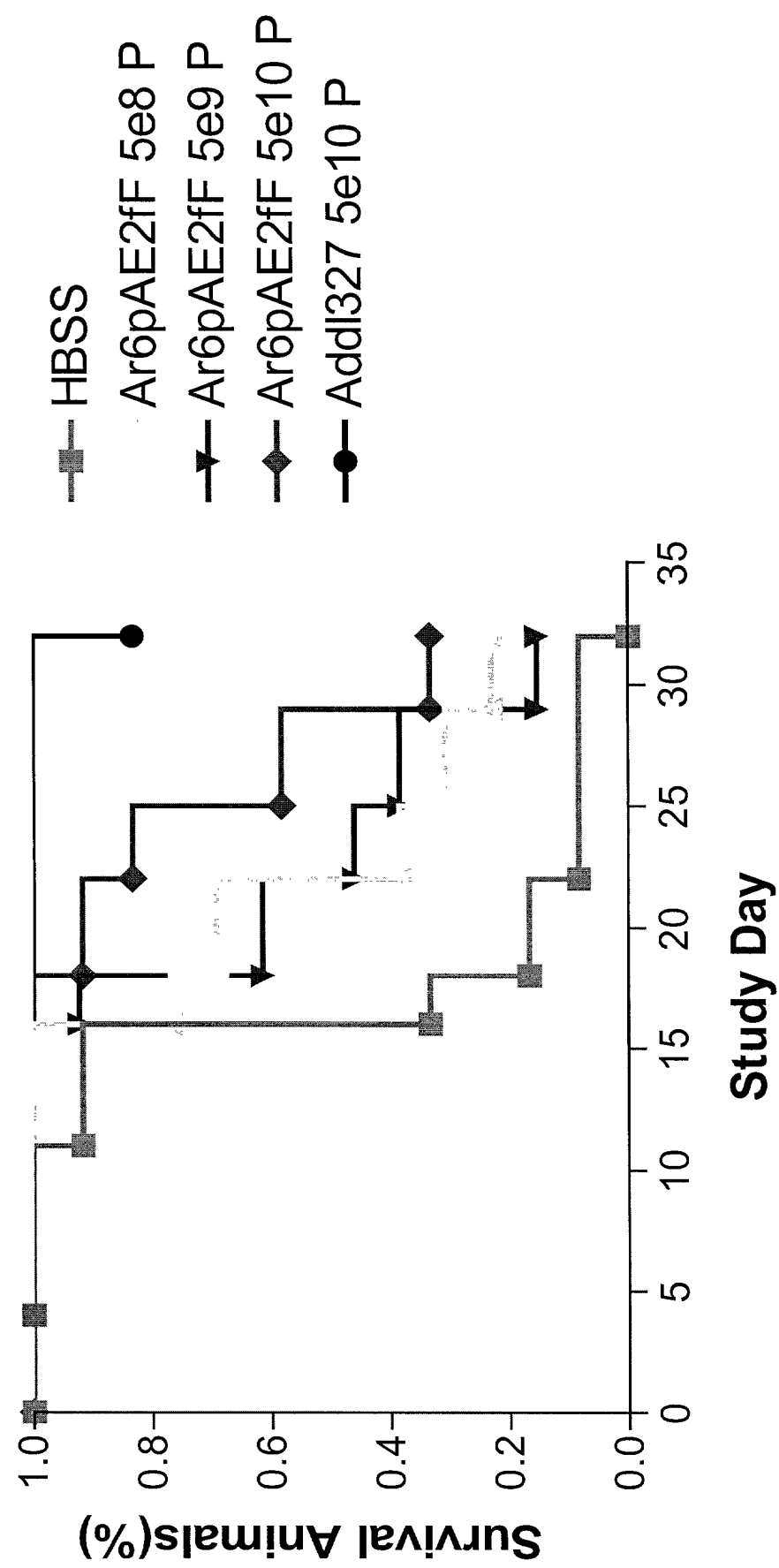
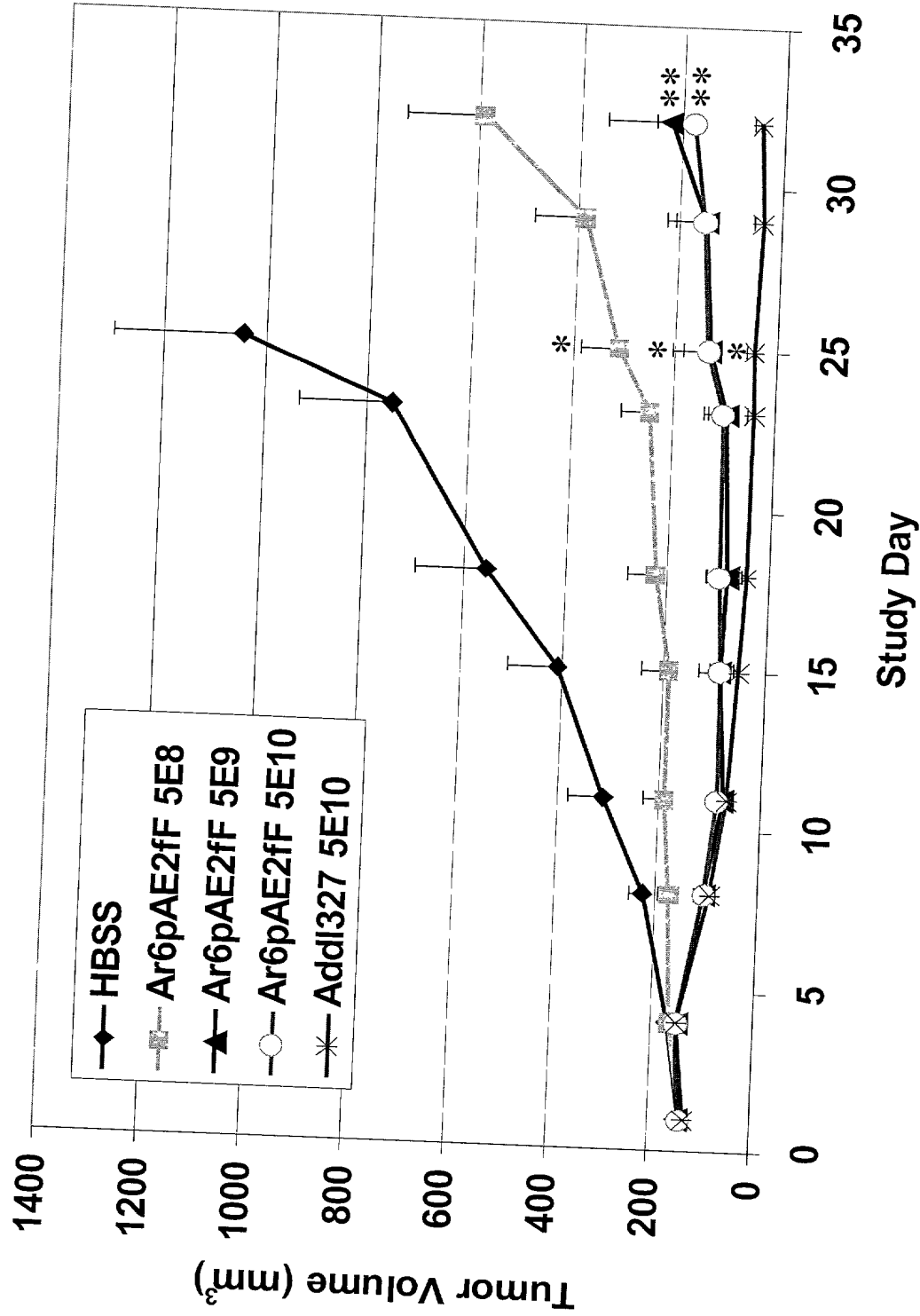


Figure 10. Survival following intratumoral administration of vectors to H460 tumors



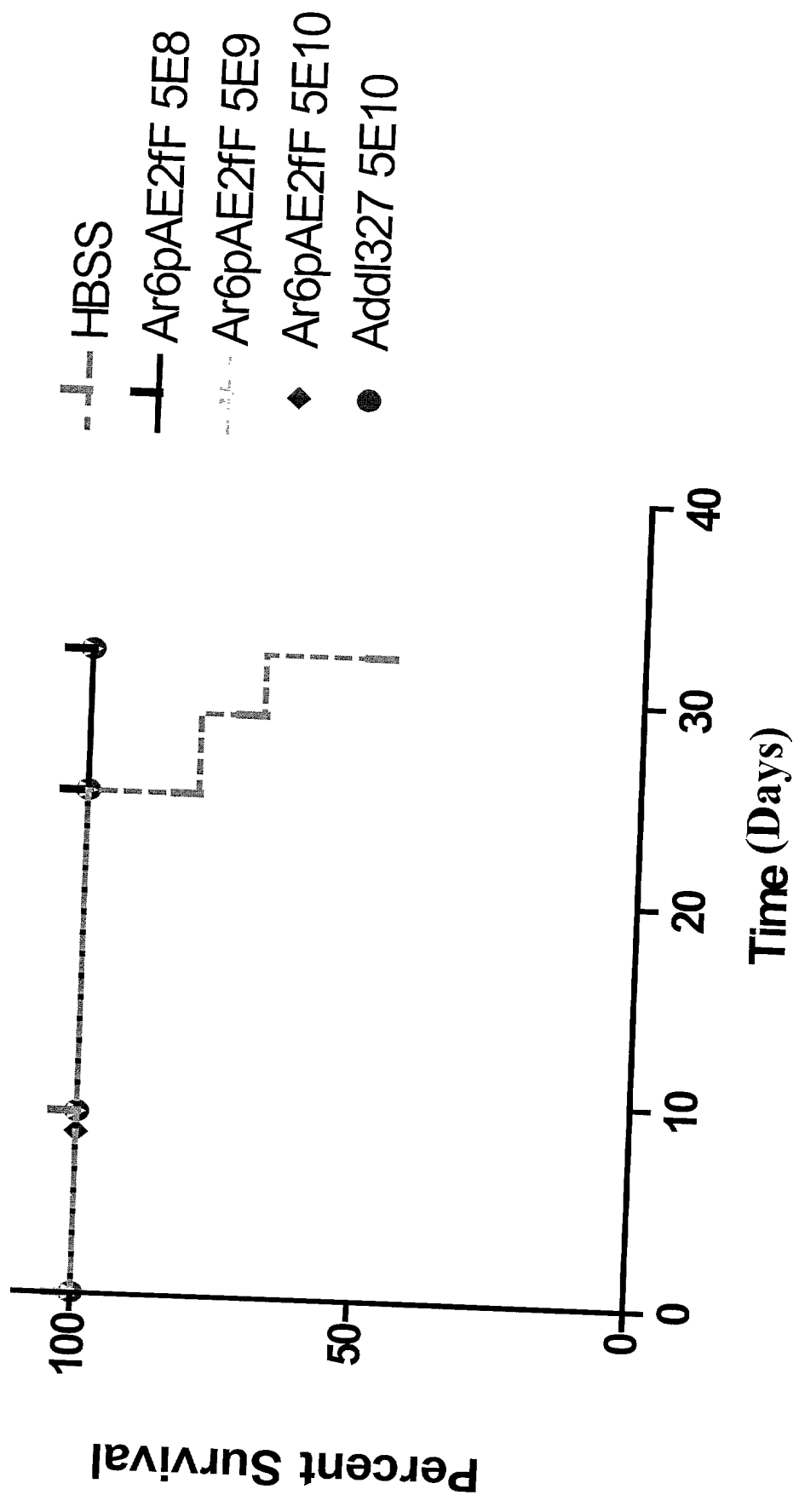
13/73

Figure 11. Mean Hep3B tumor volumes



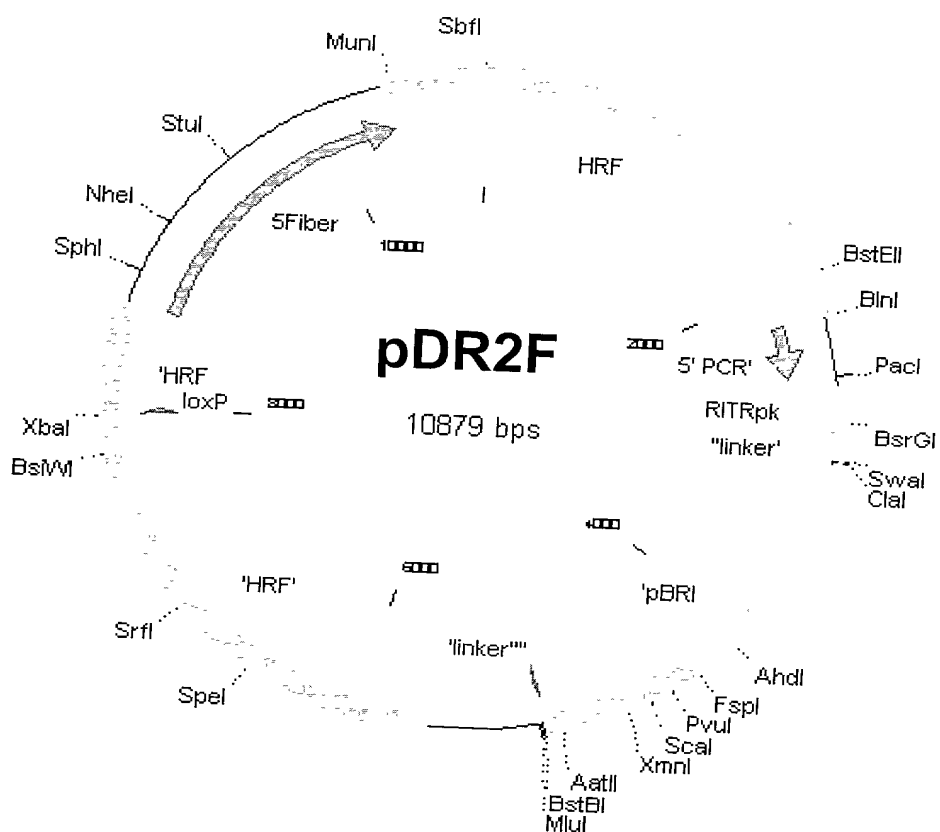
14/73

Figure 12. Survival following intratumoral administration of vector to Hep3B tumors



15/73

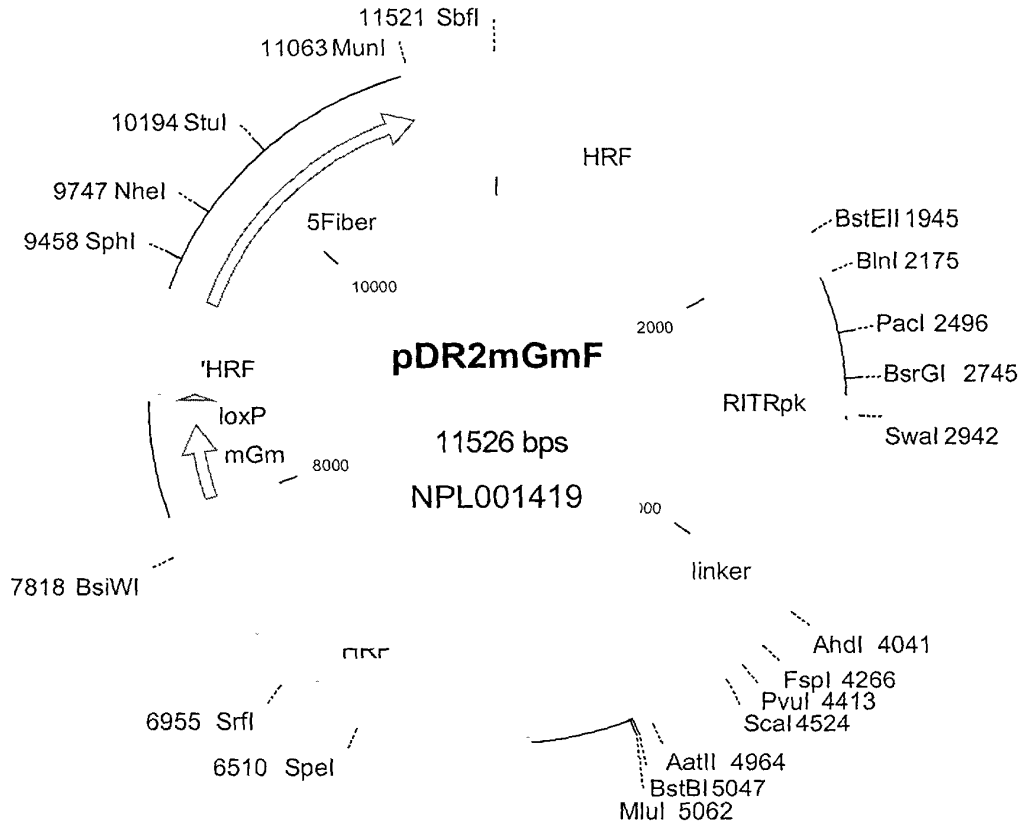
Figure 13. Schematic diagram of adenovirus right donor plasmid pDR2F.



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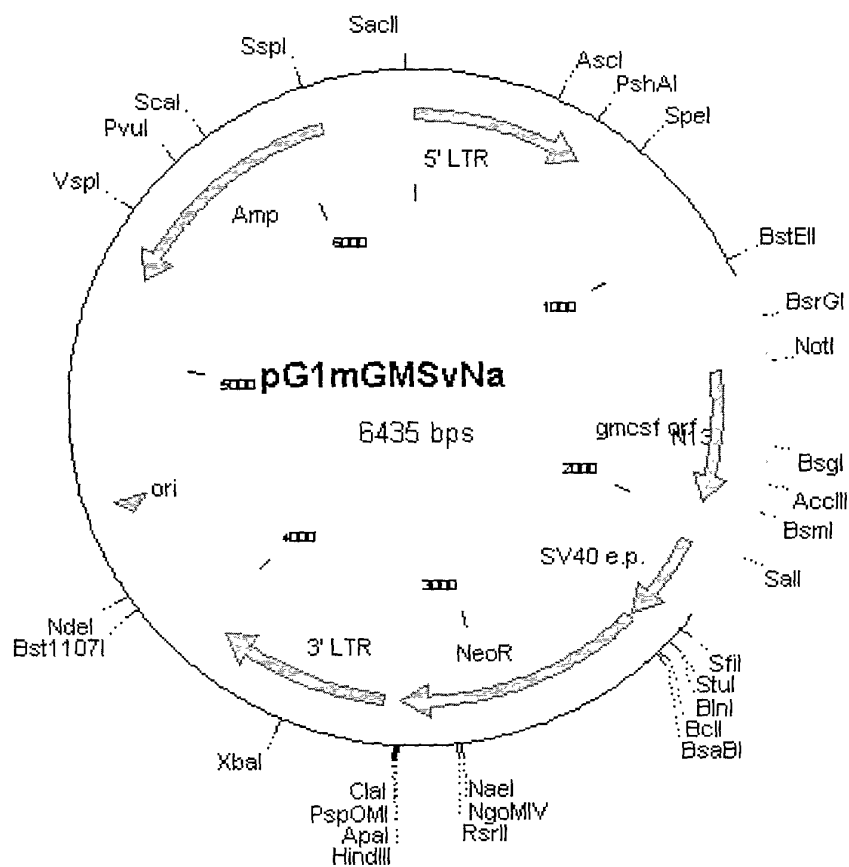
16/73

Figure 14. Schematic diagram of adenovirus right donor plasmid pDR2mGmF.



17/73

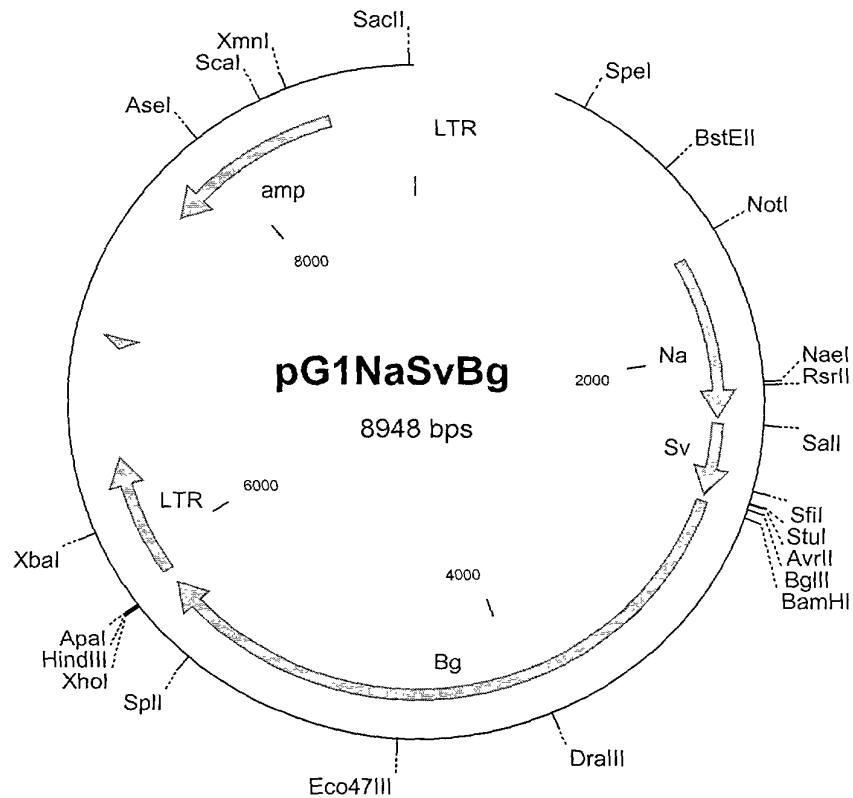
Figure 15. Schematic diagram of plasmid pG1mGmSvNa.



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18/73

Figure 16. Schematic diagram of plasmid pG1NaSvBg.



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Figure 17. Sequence of the murine GM-CSF cDNA (Seq ID NO:7) and protein (Seq ID NO:8).

7878 TTCCGGACAG ACCTCAATAA CTCTGTTTAC CAGAACAGGA GGTGAGCTTA
7928 GAAAACCCTT AGGGTATTAG GCCAAAGGCG CAGCTACTGT GGGGTTTATG
7978 AACAATTCAA GCAACTCTAC GGGCTATTCT AATTCAGGTT TCTCTAGCCG
8028 GGCTGCAGGA ATTCGATGGC CGCTACCTAC AATGGCCCAC GAGAGAAAGG
M A H E R K
8078 CTAAGGTCCT GAGGAGGATG TGGCTGCAGA ATTTACTTTT CCTGGGCATT
A K V L R R M W L Q N L L F L G I
8128 GTGGTCTACA GCCTCTCAGC ACCCACCCGC TCACCCATCA CTGTCACCCG
V V Y S L S A P T R S P I T V T
8178 GCCTTGGAAG CATGTAGAGG CCATCAAAGA AGCCCTGAAC CTCCTGGATG
R P W K H V E A I K E A L N L L D
8228 ACATGCCTGT CACATTGAAT GAAGAGGTAG AAGTCGTCTC TAACGAGTTC
D M P V T L N E E V E V V S N E F
8278 TCCTTCAAGA AGCTAACATG TGTGCAGACC CGCCTGAAGA TATTCGAGCA
S F K K L T C V Q T R L K I F E
8328 GGGTCTACGG GGCAATTTCA CCAAACCTCAA GGGCGCCTTG AACATGACAG
Q G L R G N F T K L K G A L N M T
8378 CCAGCTACTA CCAGACATAC TGCCCCCCTAA CTCCGGAAAC GGACTGTGAA
A S Y Y Q T Y C P P T P E T D C E
8428 ACACAAGTTA CCACCTATGC GGATTTTCATA GACAGCCTTA AAACCTTTCT
T Q V T T Y A D F I D S L K T F
8478 GACTGATATC CCCTTTGAAT GCAAAAAACC AGTCCAAAAA TGAGGAAGCC
L T D I P F E C K K P V Q K -
8528 CAGGCCAGCT CTGAATCCAG CTTCTCAGAC TGCTGCTTTT GTGCCTGCGT
8578 AATGAGCCAG GAACTCGGAA TTTCTGCCTT AAAGGGACCA AGAGATGTGG
8628 CACAGGTAGT CGAATCAAGC TTATCGATAC CGTCGACCTC GACTAGATAA
8678 CTTTCGTATAA TGTATGCTAT ACGAAGTTAT GCTAGAAATG GACGGAATTA
8728 TTACAGAGCA GCGCCTGCTA GAAAGACGCA GGGCAGCGGC CGAGCAACAG
8778 CGCATGAATC AAGAGCTCCA AGACATGGTT AACTTGCACC AGTGCAAAA 8826

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20/73

Figure 18. Pathway used to generate pAr6pAE2fmGmF plasmid.

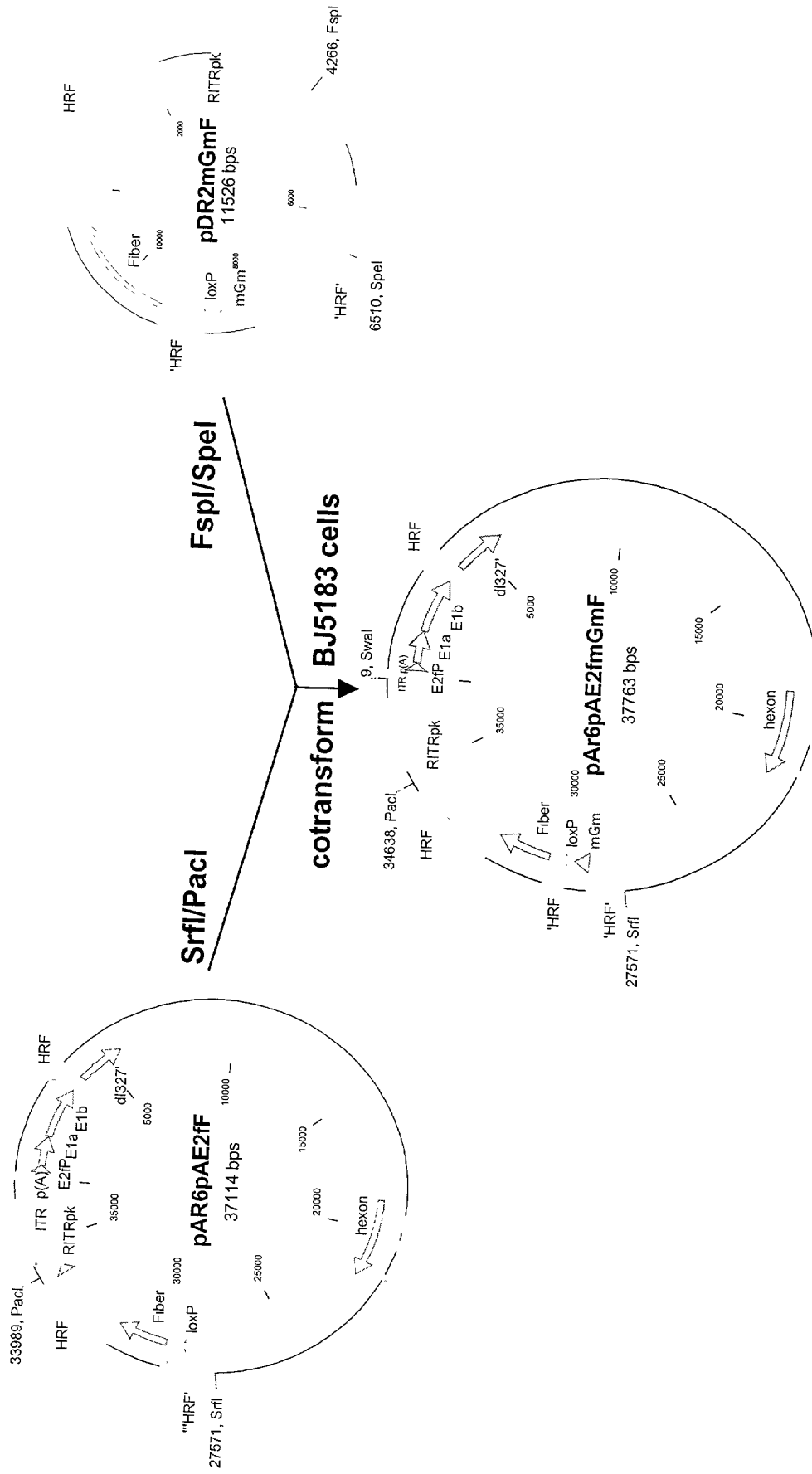


Figure 19. MTS assay of oncolytic vectors on different tumor cell lines.

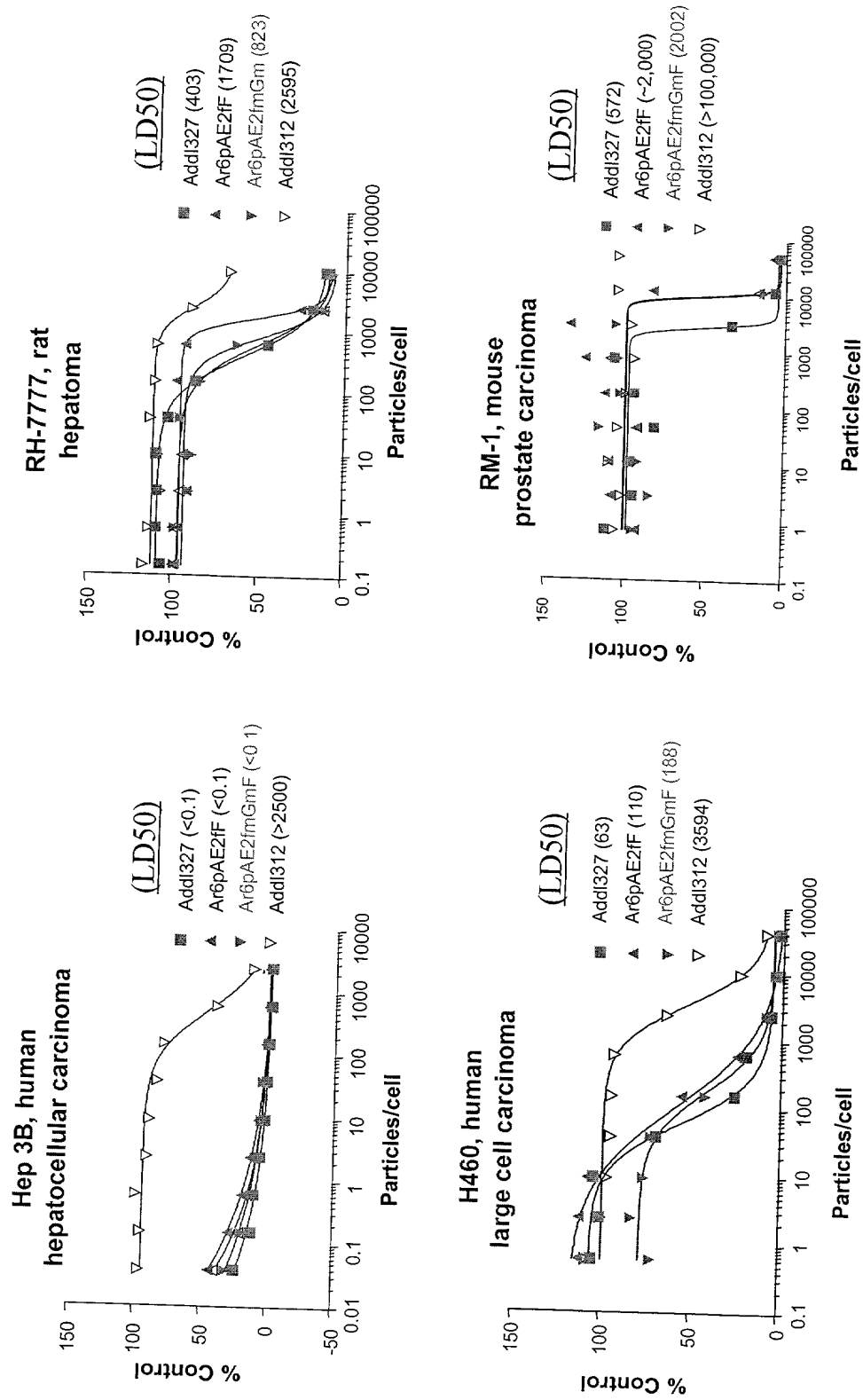


Figure 20. Sequence of the human GM-CSF cDNA (Seq ID NO:19) and protein (Seq ID NO:20).

28536 TATTAGGCCA AAGGCGCAGC TACTGTGGGG TTTATGAACA ATTCAAGCAA
28586 CTCTACGGGC TATTCTAATT CAGGTTTCTC TAGGATCTTT CCGCAGCAGC

28636 CGCCACCATG TGGCTGCAGA GCCTGCTGCT CTTGGGCACT GTGGCCTGCA
M W L Q S L L L L G T V A C

28686 GCATCTCTGC ACCCGCCCCG CCGCCAGCC CCAGCACGCA GCCCTGGGAG
S I S A P A R S P S P S T Q P W E

28736 CATGTGAATG CCATCCAGGA GGCCCGGCGT CTCCTGAACC TGAGTAGAGA
H V N A I Q E A R R L L N L S R

28786 CACTGCTGCT GAGATGAATG AAACAGTAGA AGTCATCTCA GAAATGTTTG
D T A A E M N E T V E V I S E M F

28836 ACCTCCAGGA GCCGACCTGC CTACAGACCC GCCTGGAGCT GTACAAGCAG
D L Q E P T C L Q T R L E L Y K Q

28886 GGCTGCGGG GCAGCCTCAC CAAGCTCAAG GGCCCCTTGA CCATGATGGC
G L R G S L T K L K G P L T M M

28936 CAGCCACTAC AAGCAGCACT GCCCTCCAAC CCCGGAAACT TCCTGTGCAA
A S H Y K Q H C P P T P E T S C A

28986 CCCAGACTAT CACCTTTGAA AGTTTCAAAG AGAACCTGAA GGACTTTCTG
T Q T I T F E S F K E N L K D F L

29036 CTTGTCATCC CCTTTGACTG CTGGGAGCCA GTCCAGGAGT GAGTCGACAA
L V I P F D C W E P V Q E -

29086 GCTCTAGATA ACTTCGTATA ATGTATGCTA TACGAAGTTA TGCTAGAAAT
29136 GGACGGAATT ATTACAGAGC AGCGCCTGCT AGAAAGACGC AGGGCAGCGG
29186 CCGAGCAACA GCGCATGAAT CAAGAGCTCC AAGACATGGT TAACTTGCAC
29236 CAGTGCAAAA GGGGTATCTT TTGTCTGGTA AAGCAGG 29273

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Figure 21. Pathway used to generate pAr6pAE2fhGmF plasmid.

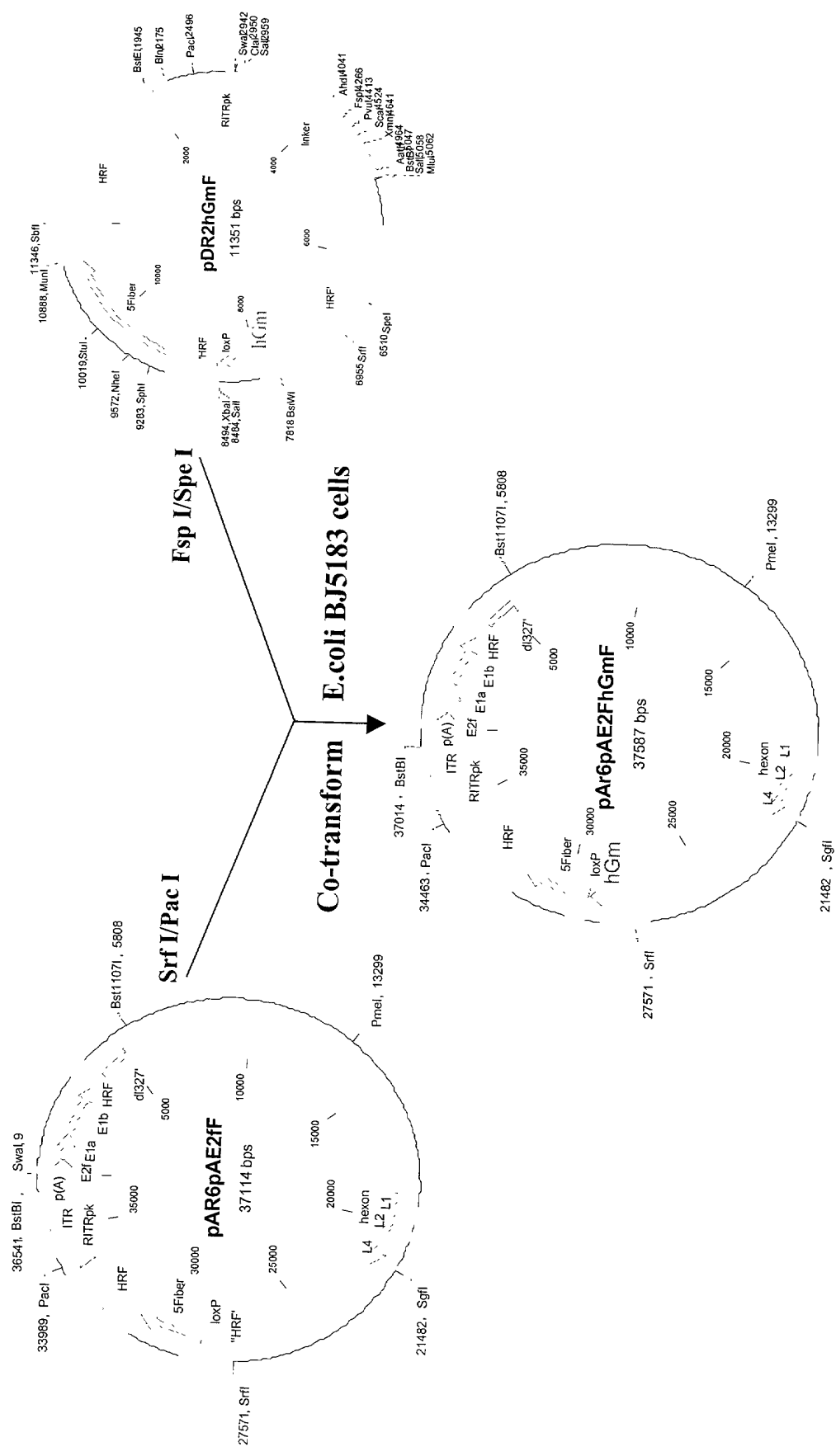
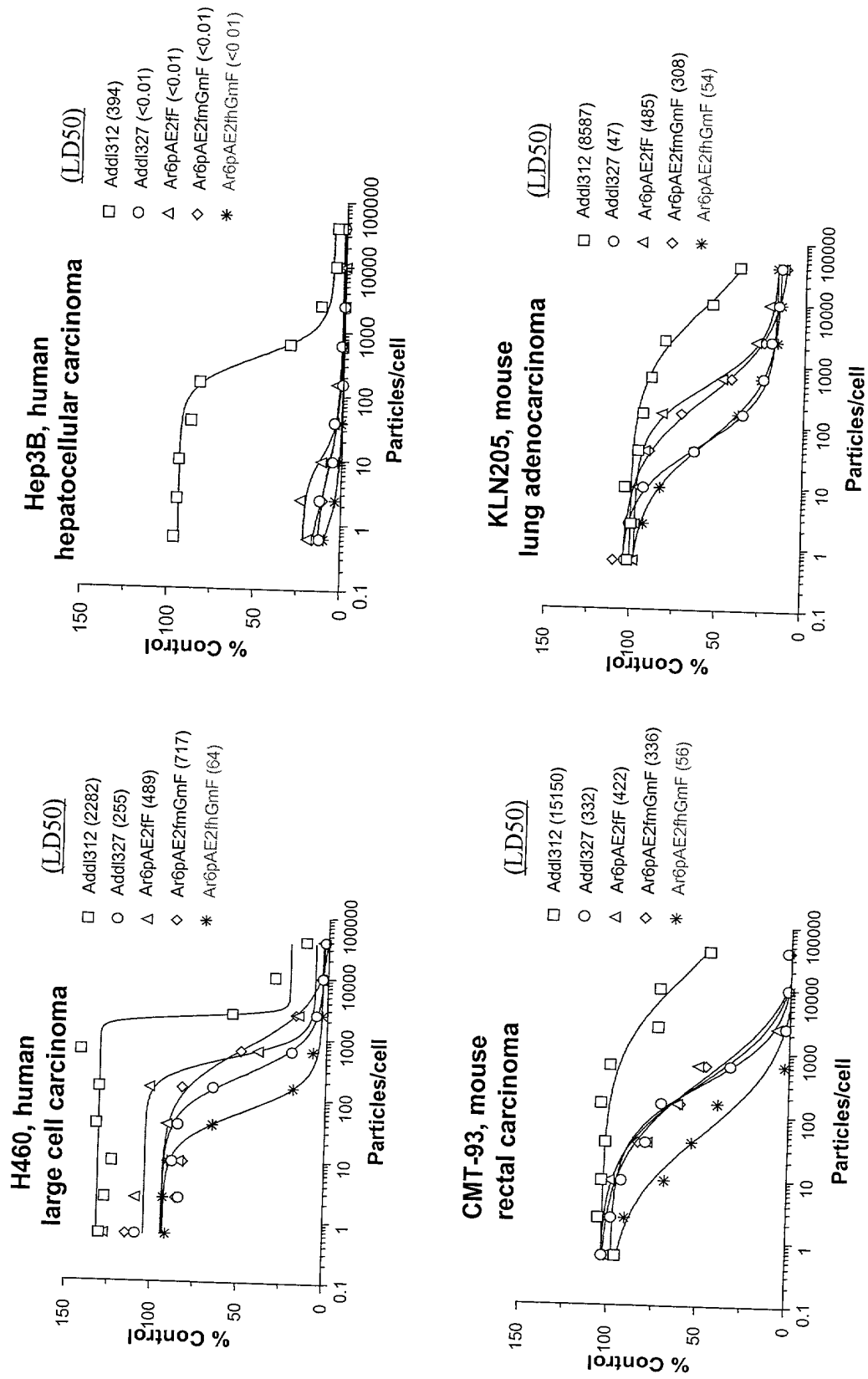


Figure 22. MTS assay of oncolytic vectors on different tumor cell lines.



25/72

Figure 23. Efficacy of GM-CSF armed oncolytic vectors in H460 tumor model

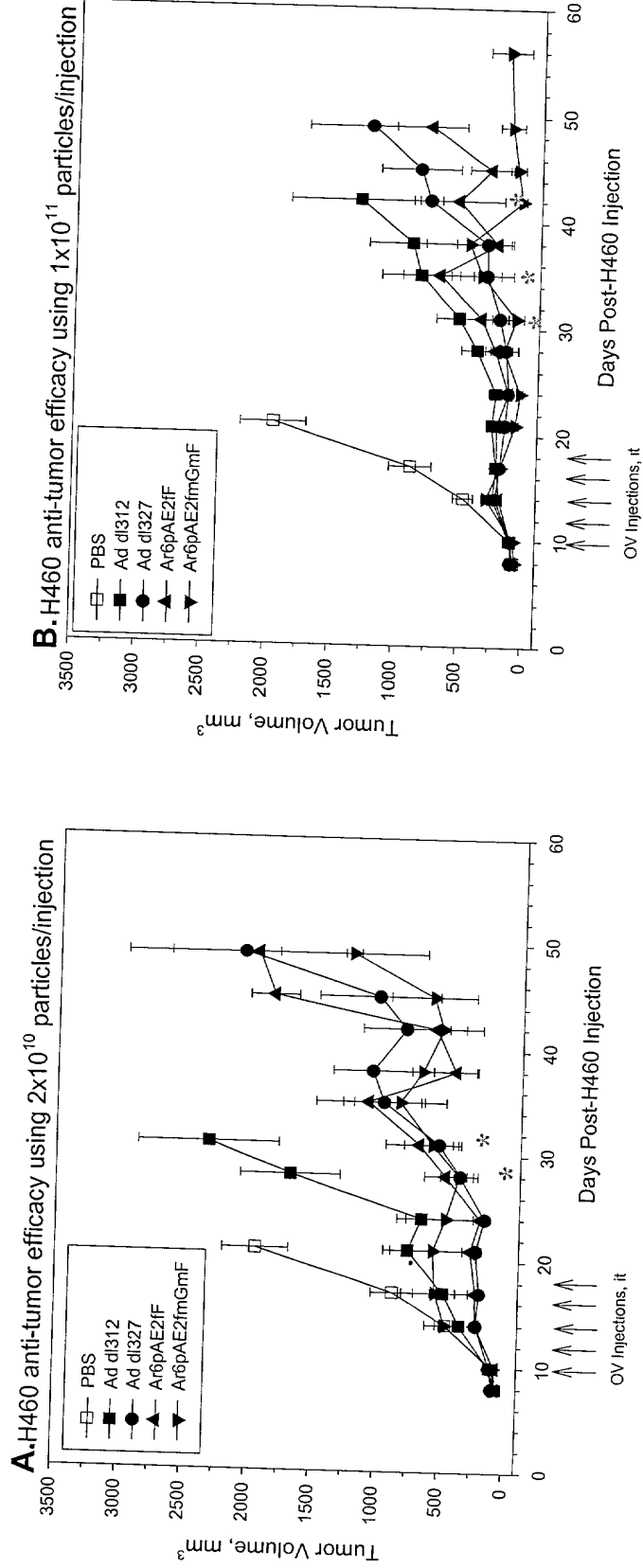


Figure 24. Efficacy of GM-CSF armed oncolytic vectors in Hep3B tumor model

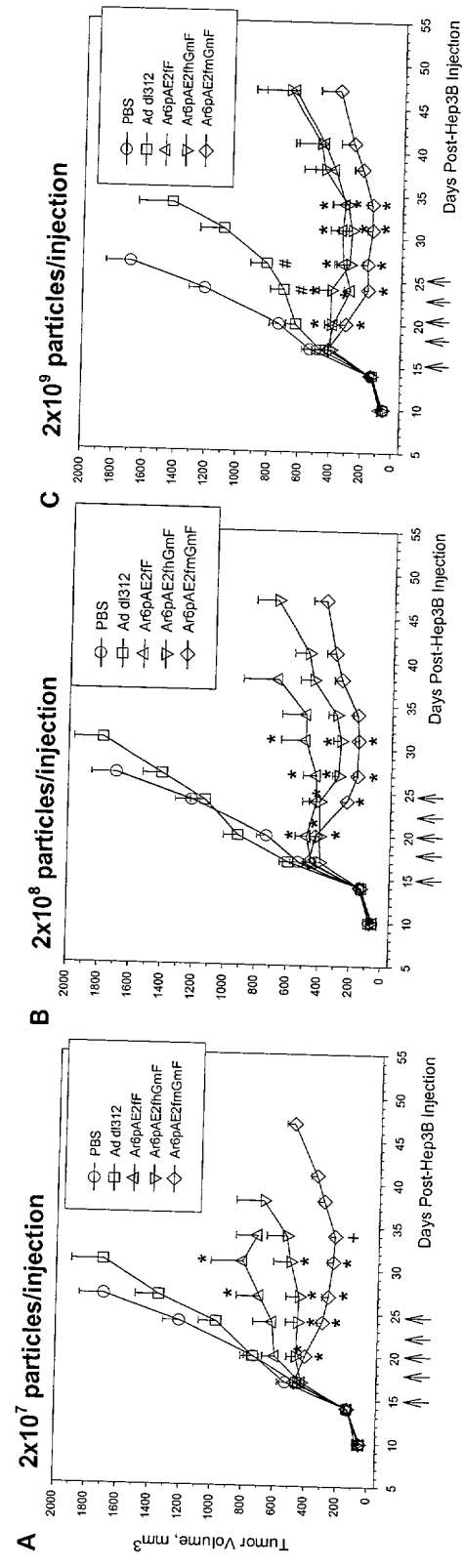
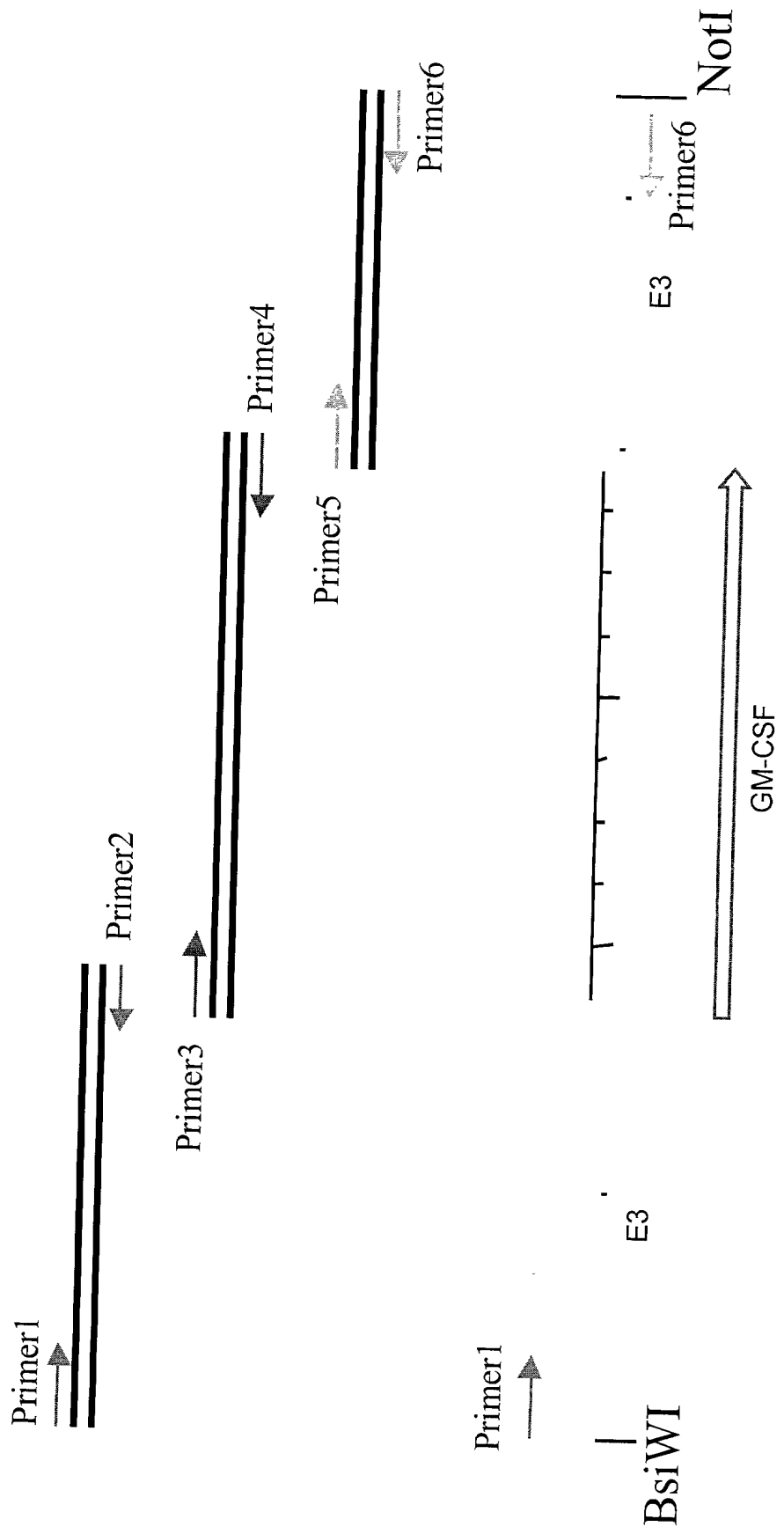


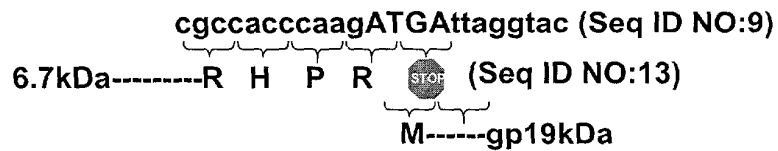
Figure 25. Schematic Diagram of PCR and Overlap PCR for Δ gp19 Donor Plasmids



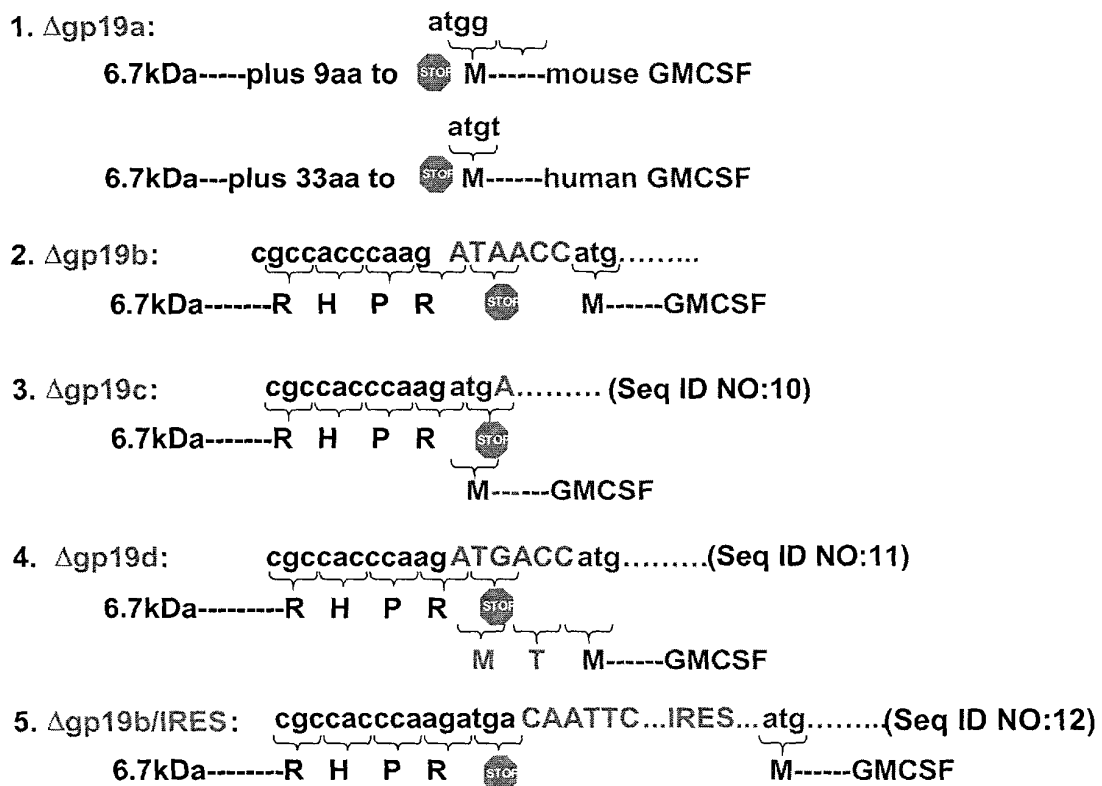
28/73

Figure 26. Schematic Diagram of Δ gp19 Vectors

a. Sequence of native E3 region:



b. Sequence comparison of Δ gp19 vectors at the junction between E3-6.7 and GM-CSF:



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Figure 27a. Pathway Used to Generate the pAr6pAE2f(E3+,mGm,Dg19b)F Large Plasmid

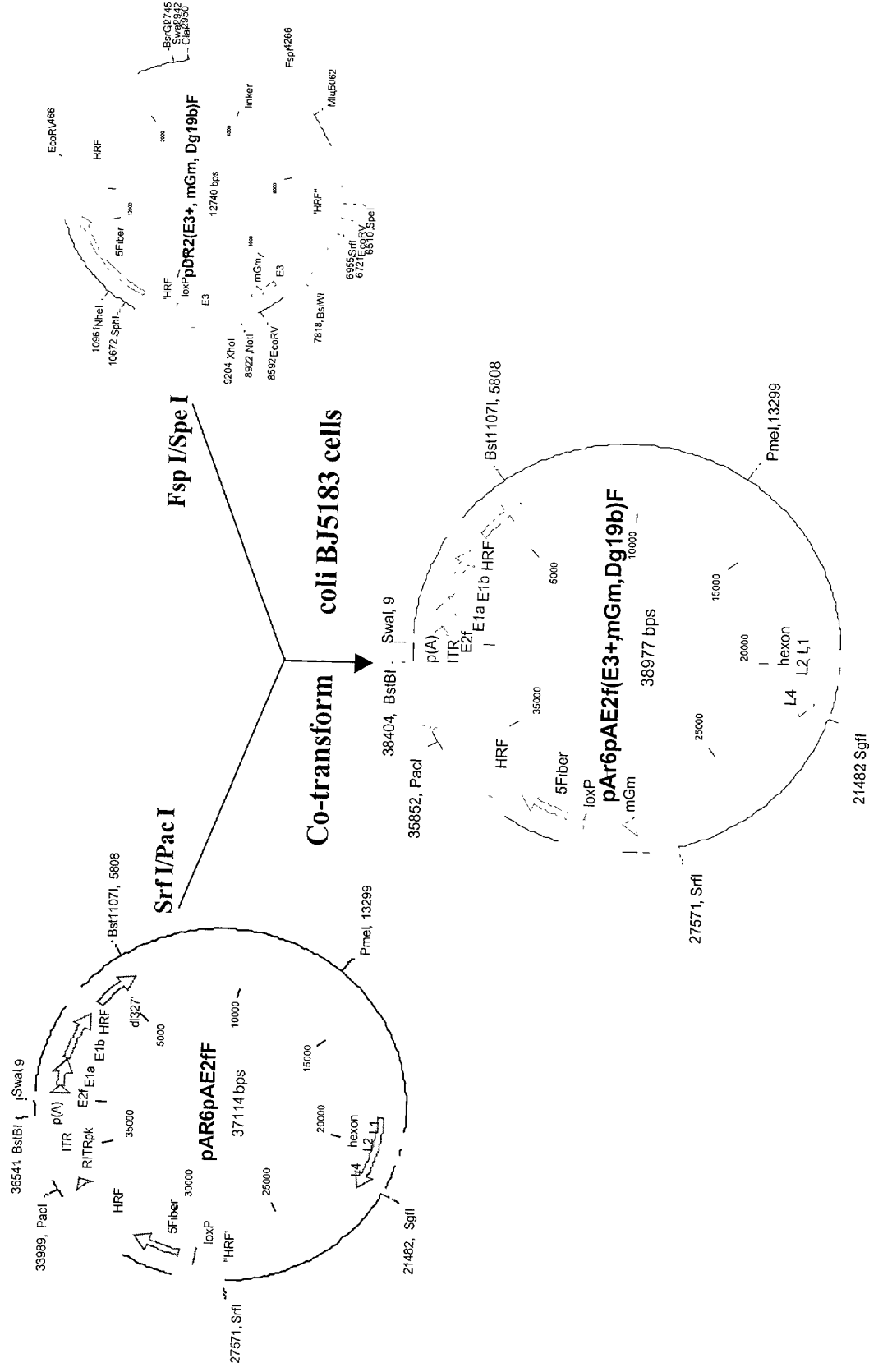


Figure 27b. Pathway Used to Generate the pAr6pAE2f(E3+,hGm,Dg19b)F Large Plasmid

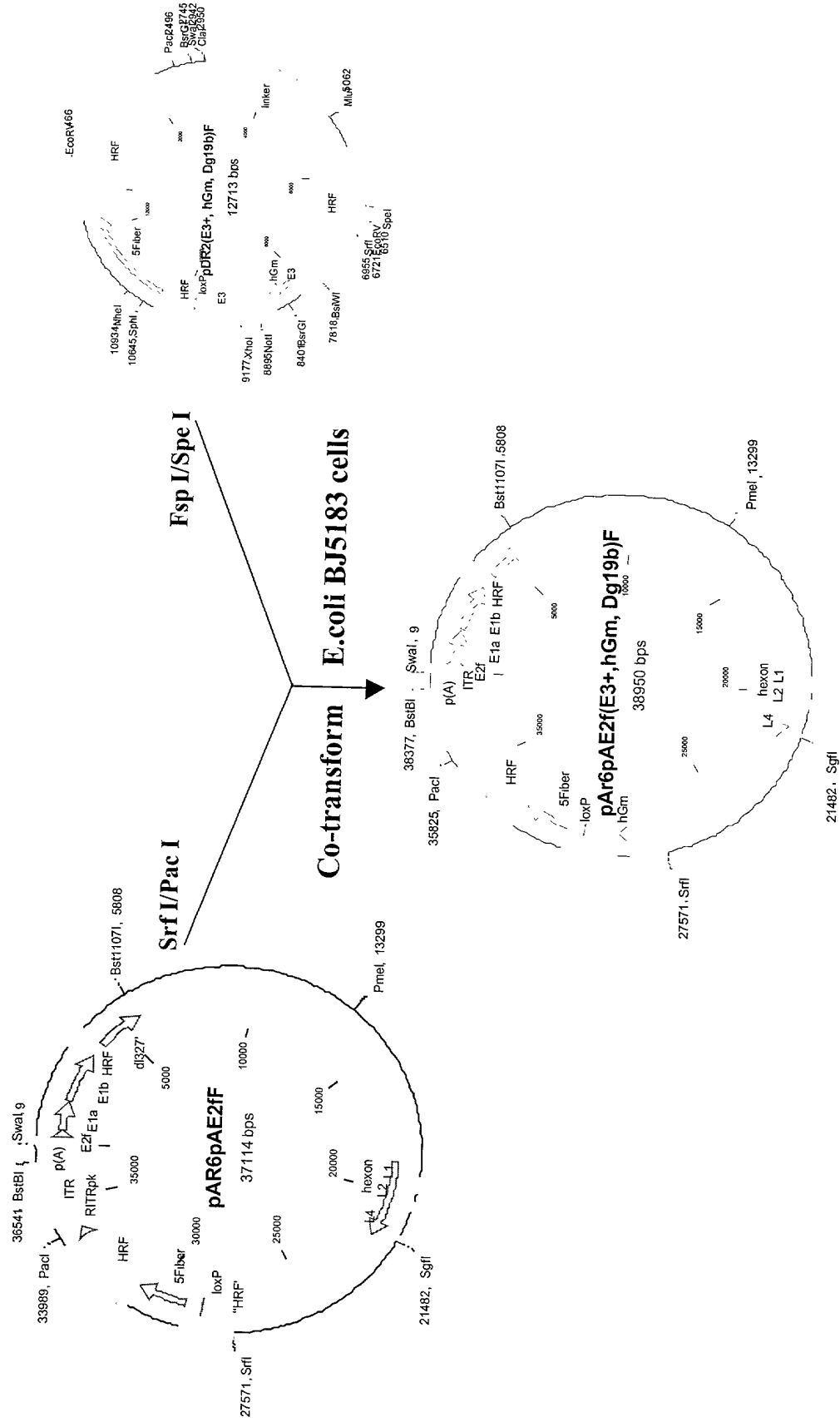


Figure 28. MTS Assay of Δ gfp19 mGM-CSF Vectors on H460 and Hep3B Tumor Cell Lines

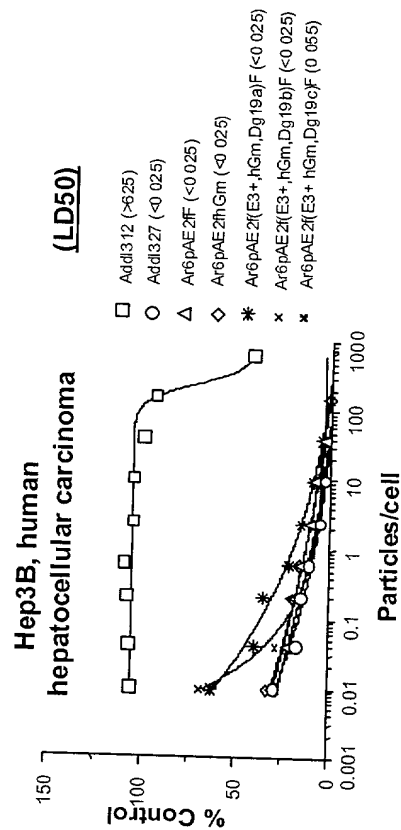
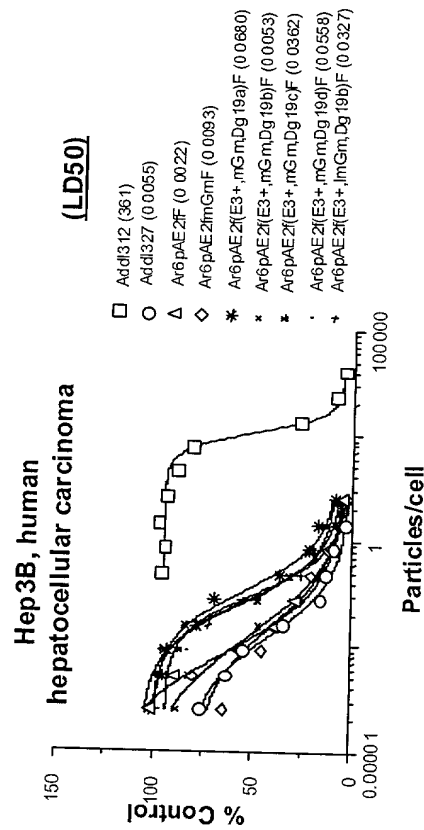
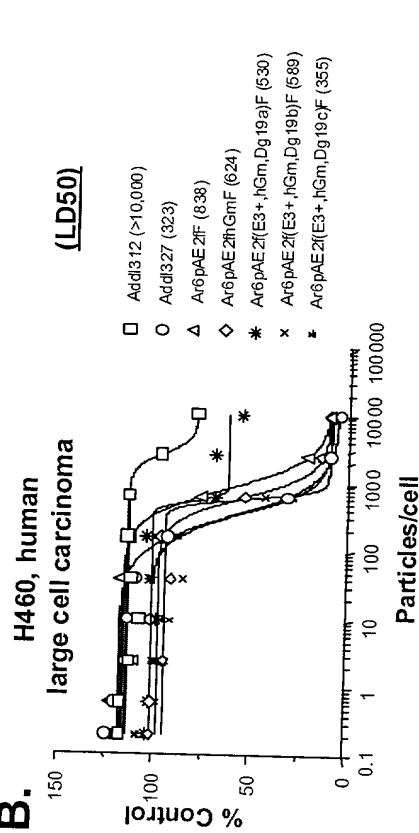
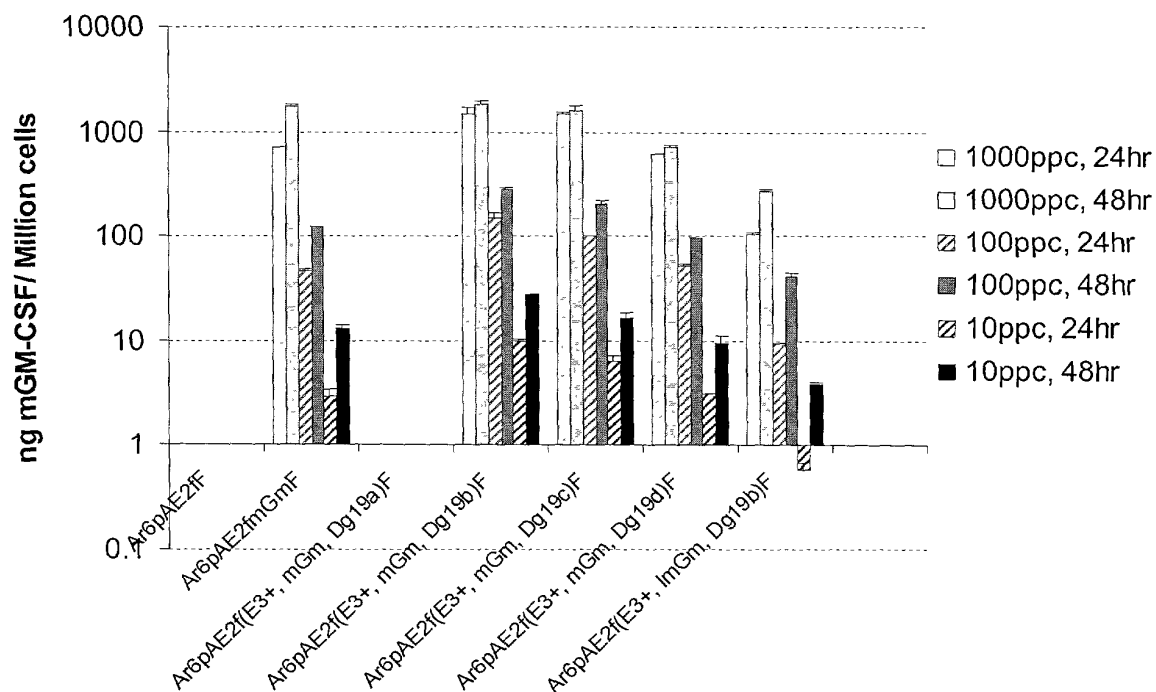


Figure 29. GM-CSF Expression Mediated by Δ gp19 GM-CSF Vectors in Infected H460 Cells Detected by ELISA

a. Mouse GM-CSF expression in H460 cells



b. Human GM-CSF expression in H460 cells

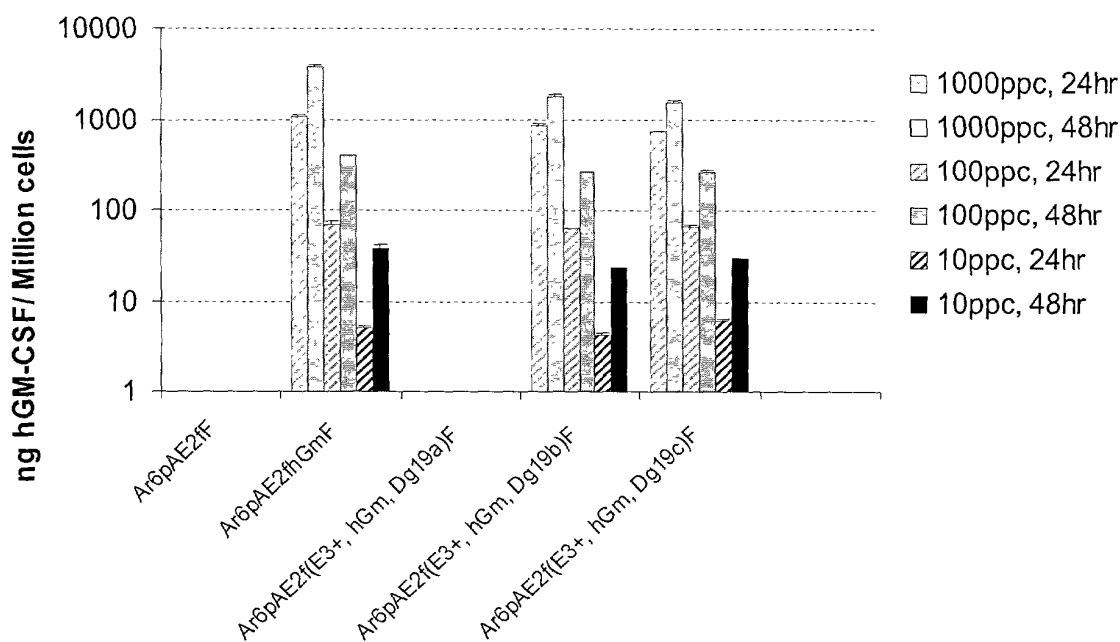


Figure 30. Anti-Tumor Activity of Oncolytic Adenoviruses (2×10^9 particles/injection) in the Hep3B Xenograft Subcutaneous Tumor Model

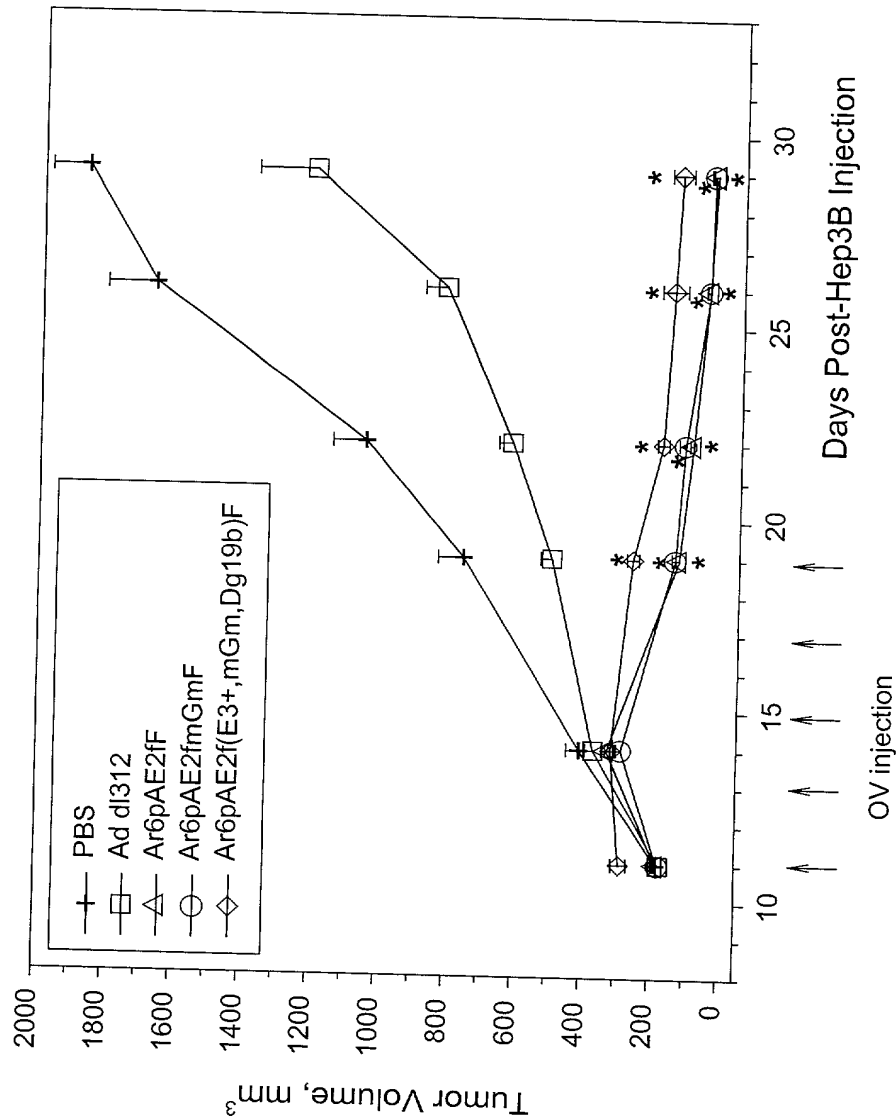
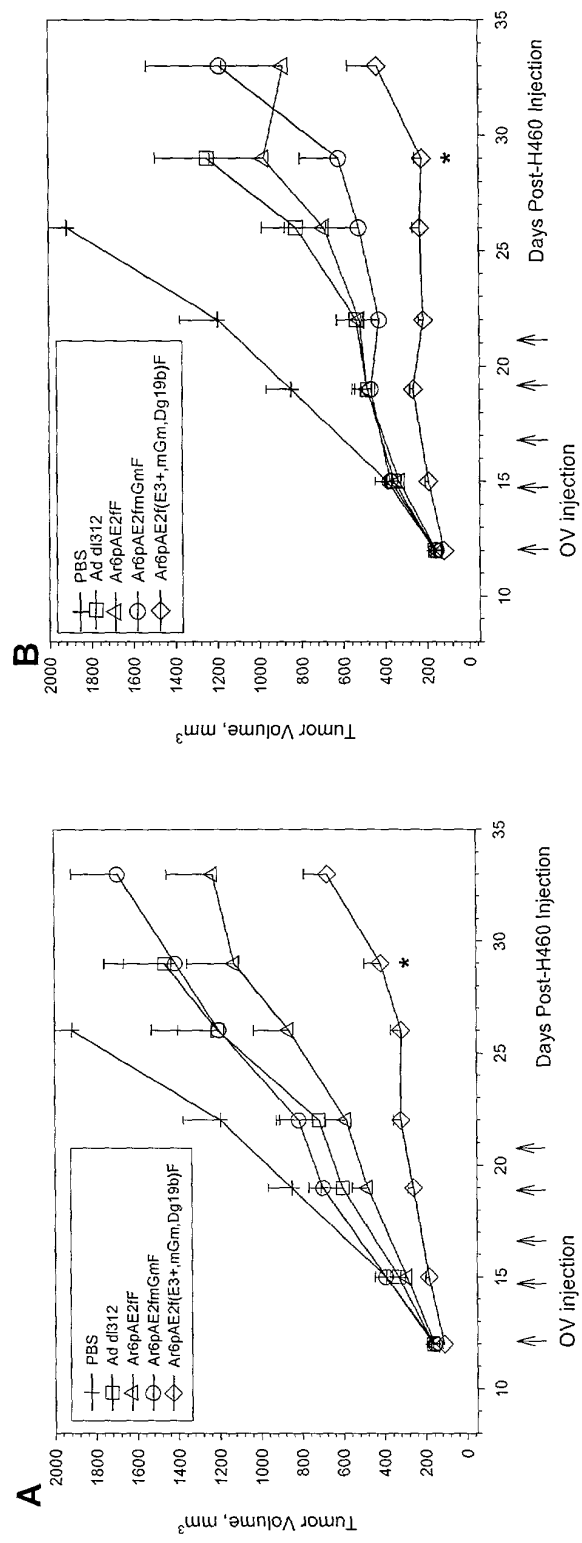


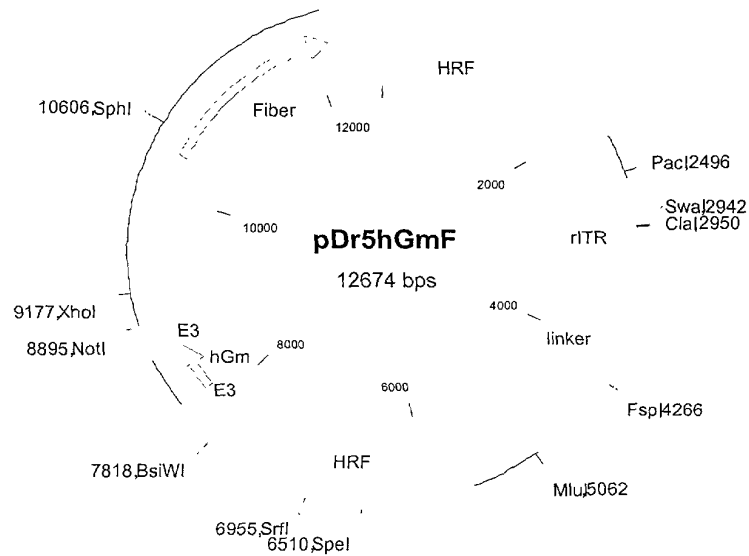
Figure 31. Anti-Tumor Activity of Oncolytic Adenoviruses in the H460 Xenograft Subcutaneous Tumor Model



35/73

Figure 32. Schematic diagram of adenovirus pDr5hGmF and pDr5mGmF right donor plasmids.

A. pDr5hGmF



B. pDr5mGmF

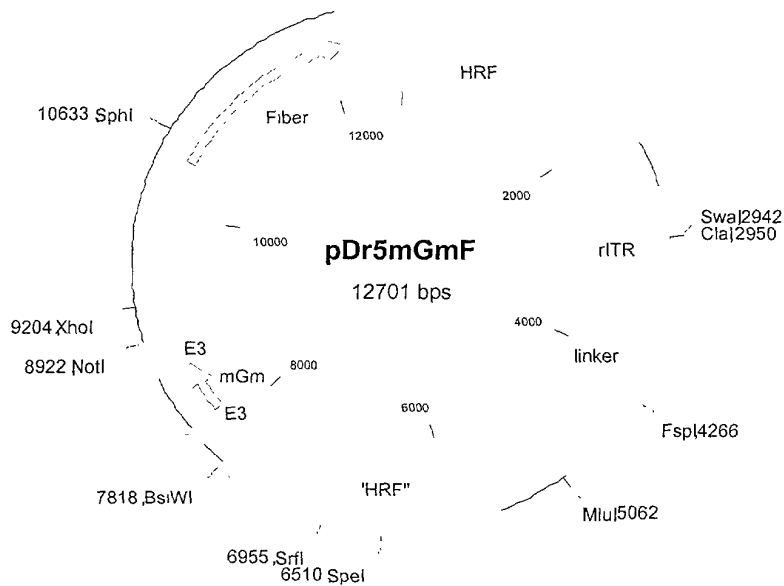


Figure 33. Pathway used to generate the pAr15pAE2fhGmF plasmid.

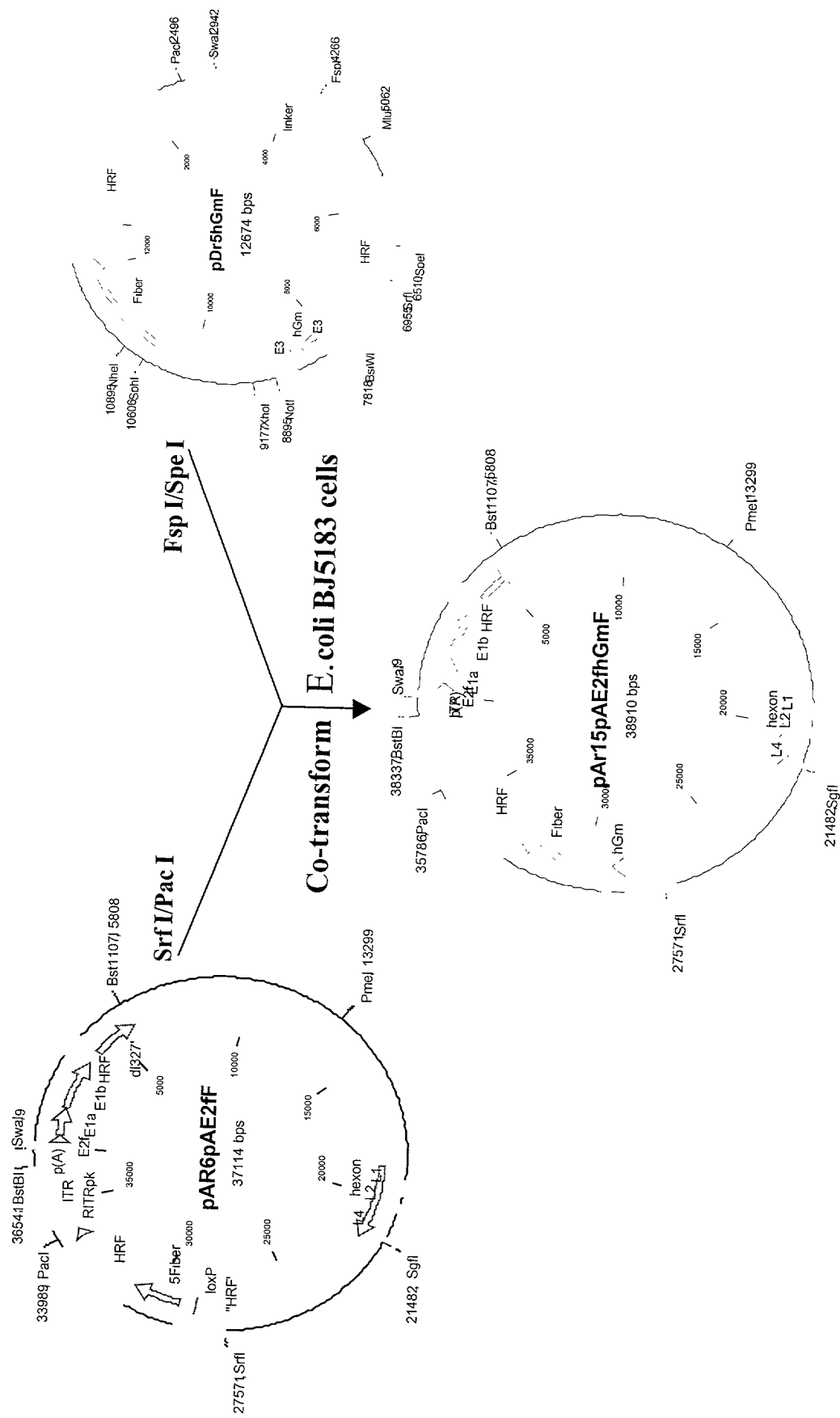


Figure 34. Pathway used to generate the pAr15pAE2fmGmF plasmid.

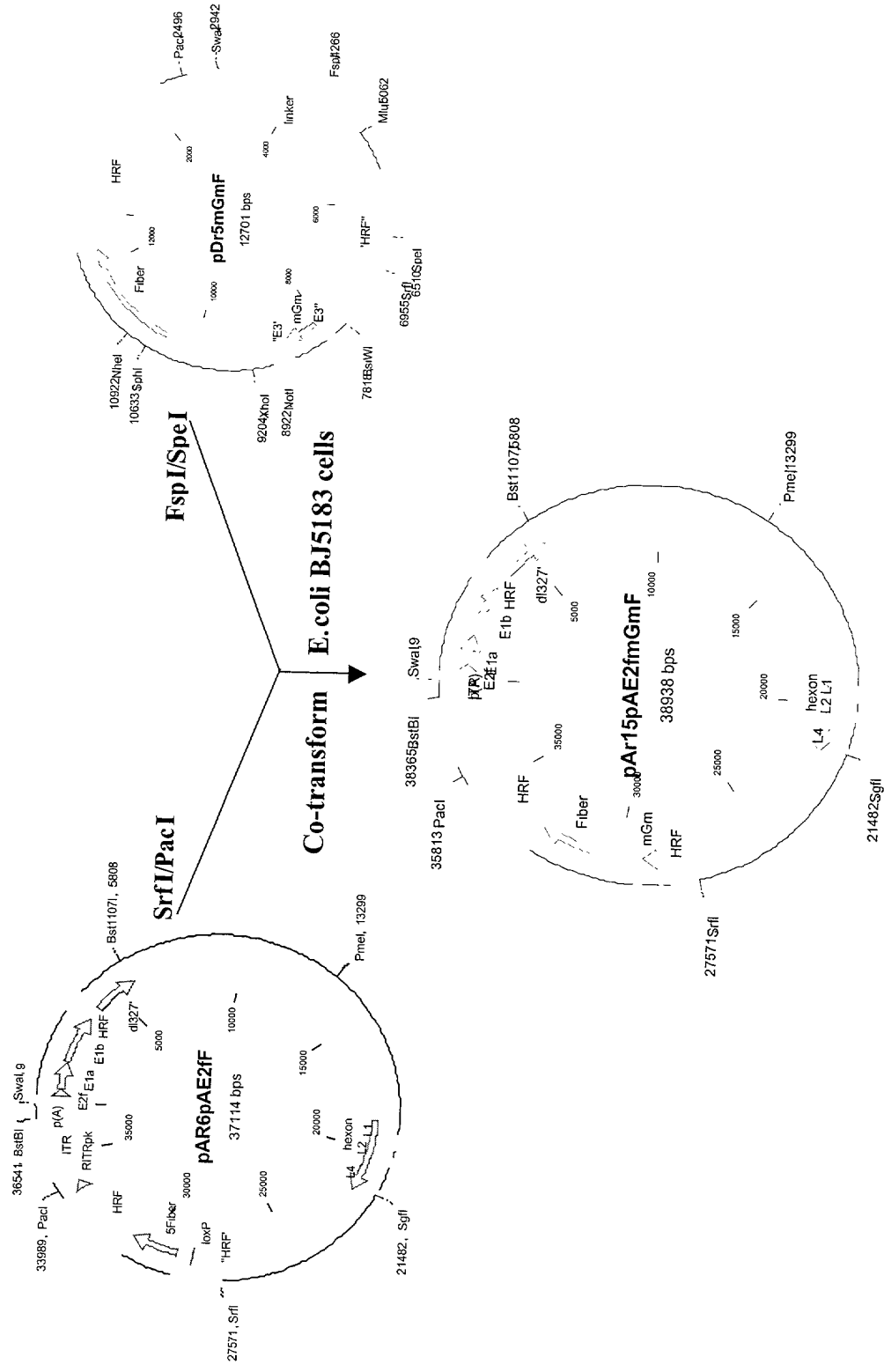
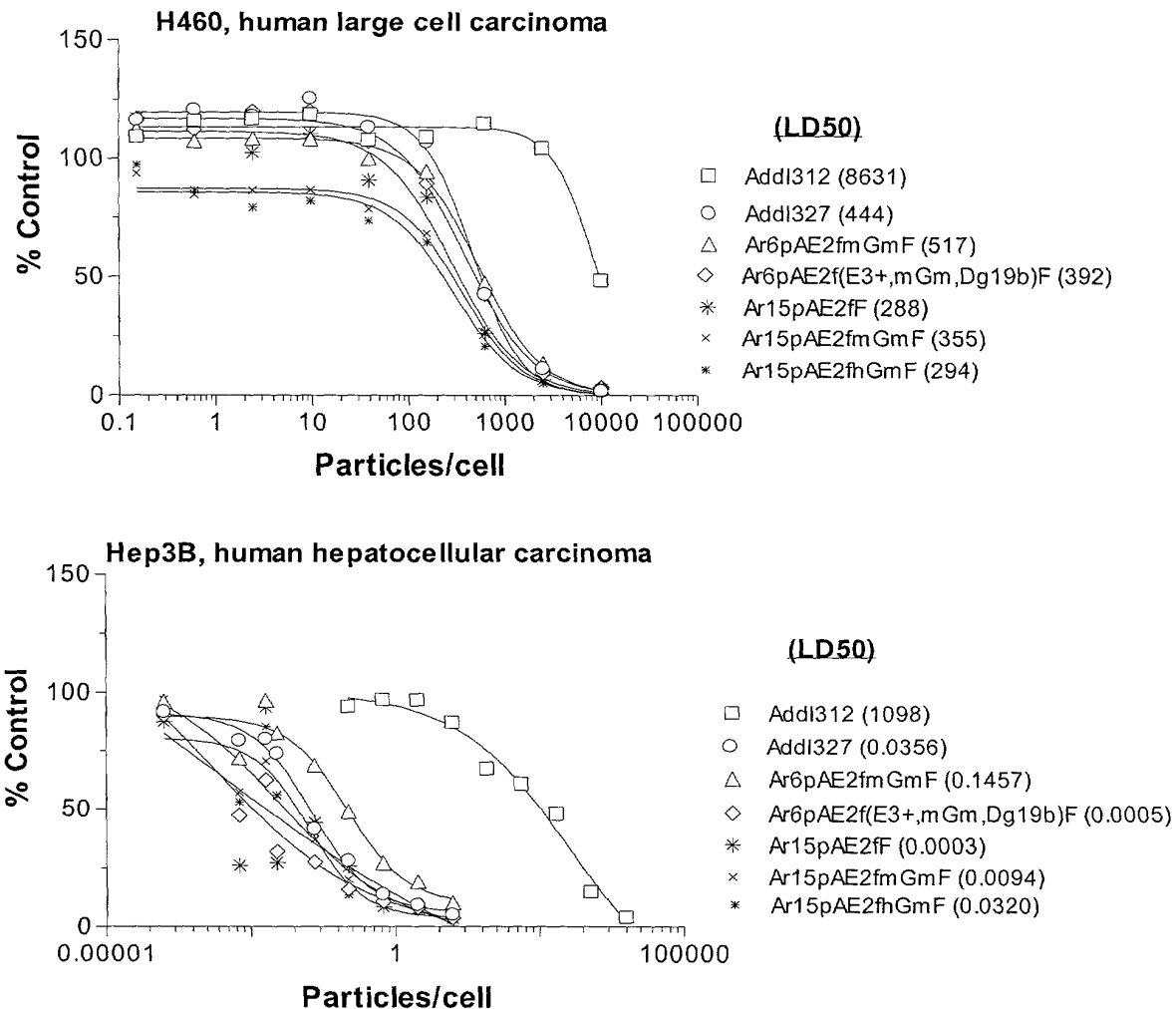
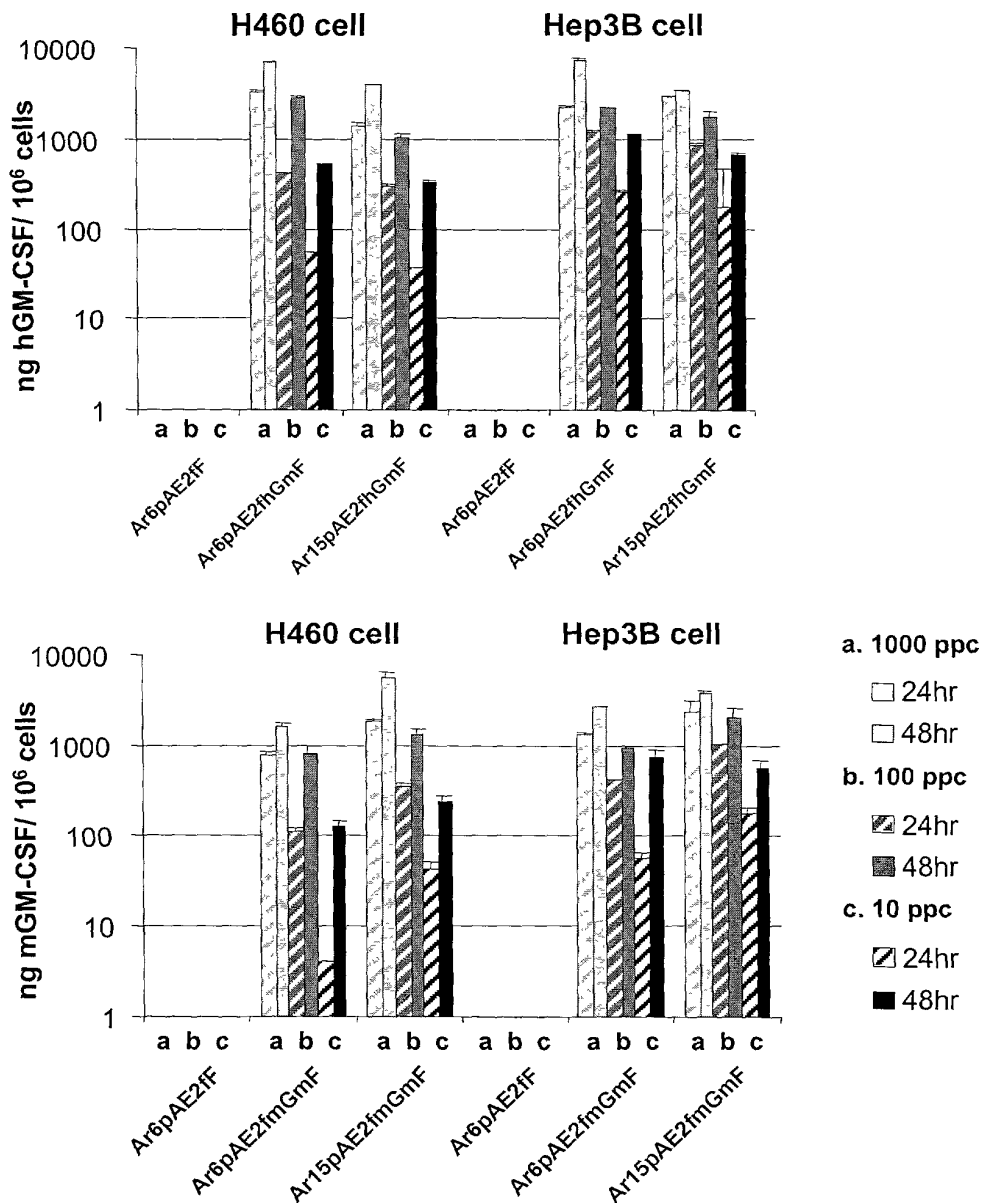


Figure 35. MTS assay of Ar15pAE2fhGmF and Ar15pAE2fmGmF vectors on H460 and Hep3B tumor cell lines.



39/73

Figure 36. GM-CSF expression mediated by Ar15pAE2fhGmF and Ar15pAE2fmGmF vectors in infected H460 cells detected by ELISA.



40/73

Figure 37. Schematic Diagram of PCR and Overlap PCR for Δ E3-14.7 plasmids

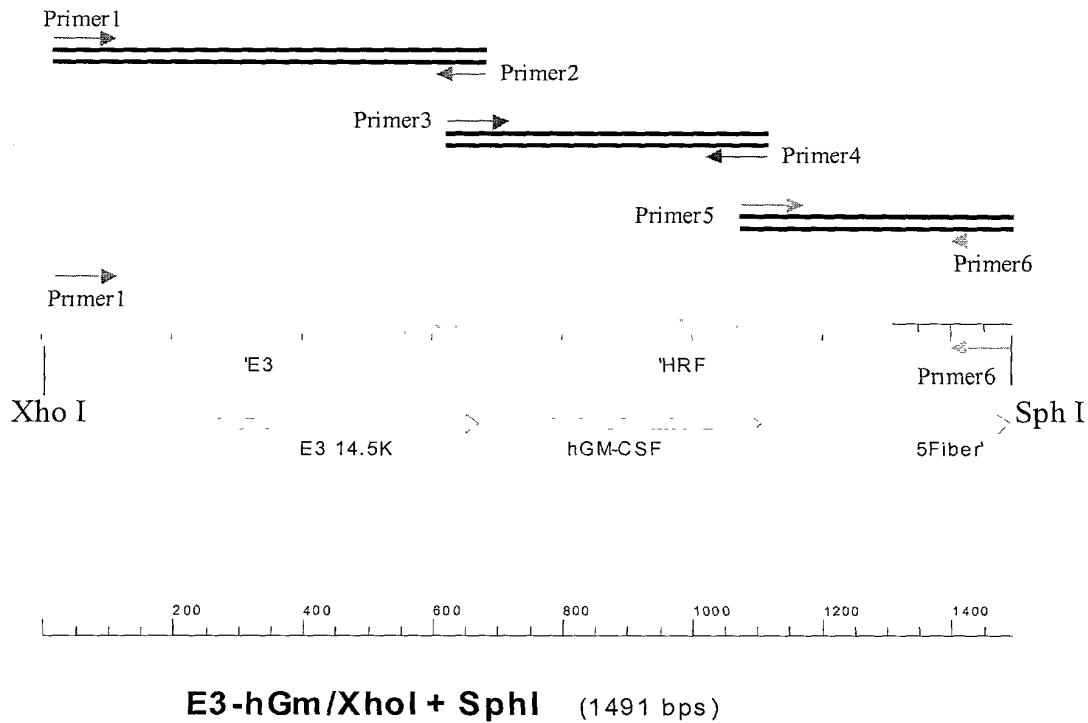


Figure 38. Schematic Diagram of ΔE3-14.7 Vectors

a. Sequence of native E3-14.5/E3-14.7 junction:

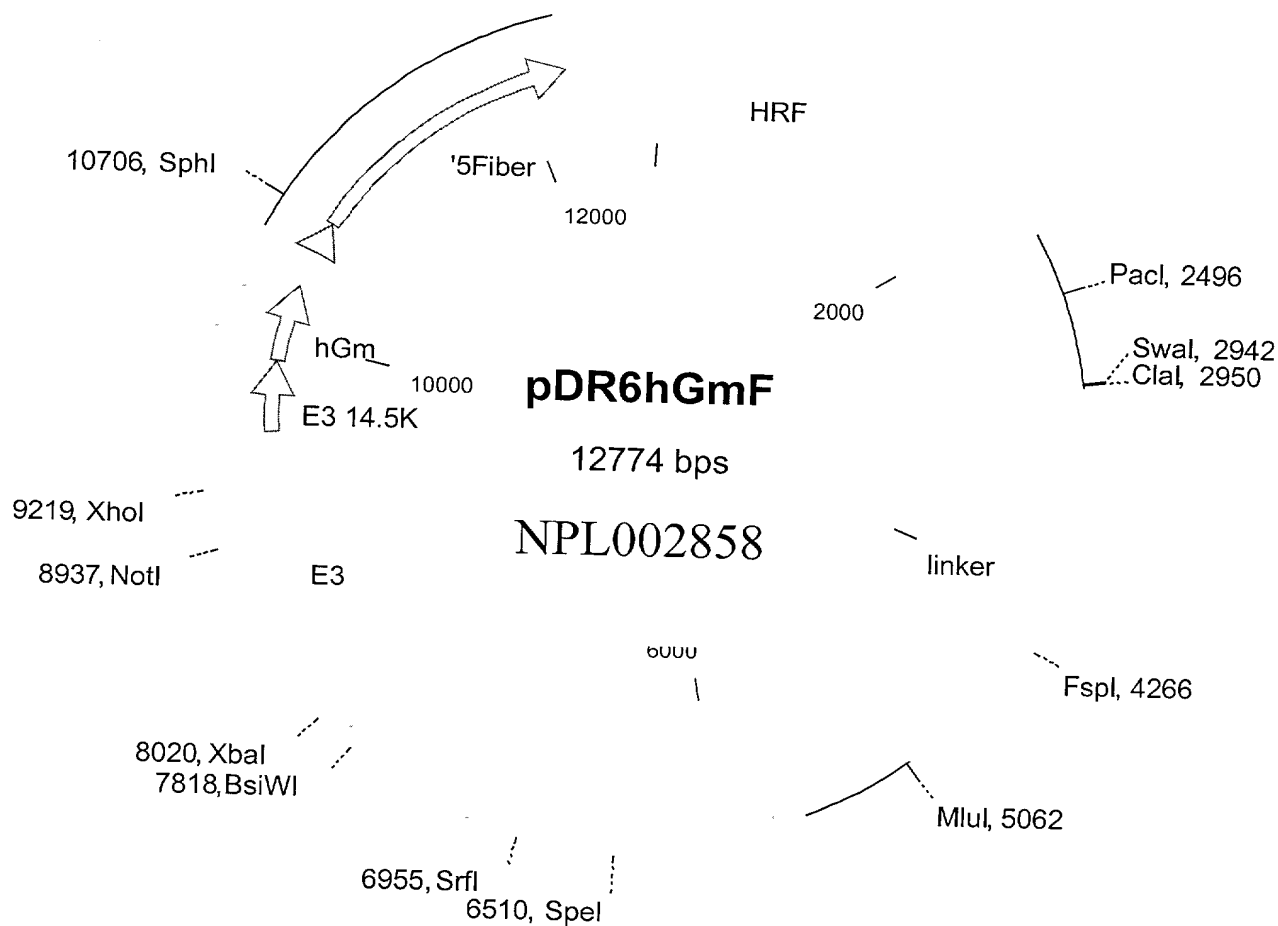


b. Sequence of the Ar16pAE2fhGm vector at the junction engineered between the E3-14.5 gene and human GM-CSF cDNA:



42/73

Figure 39. Pathway Used to Generate the pAr16pAE2fhGmF Large Plasmid



43/73

Figure 40. Pathway Used to Generate the pAr16pAE2fhGmF Large Plasmid

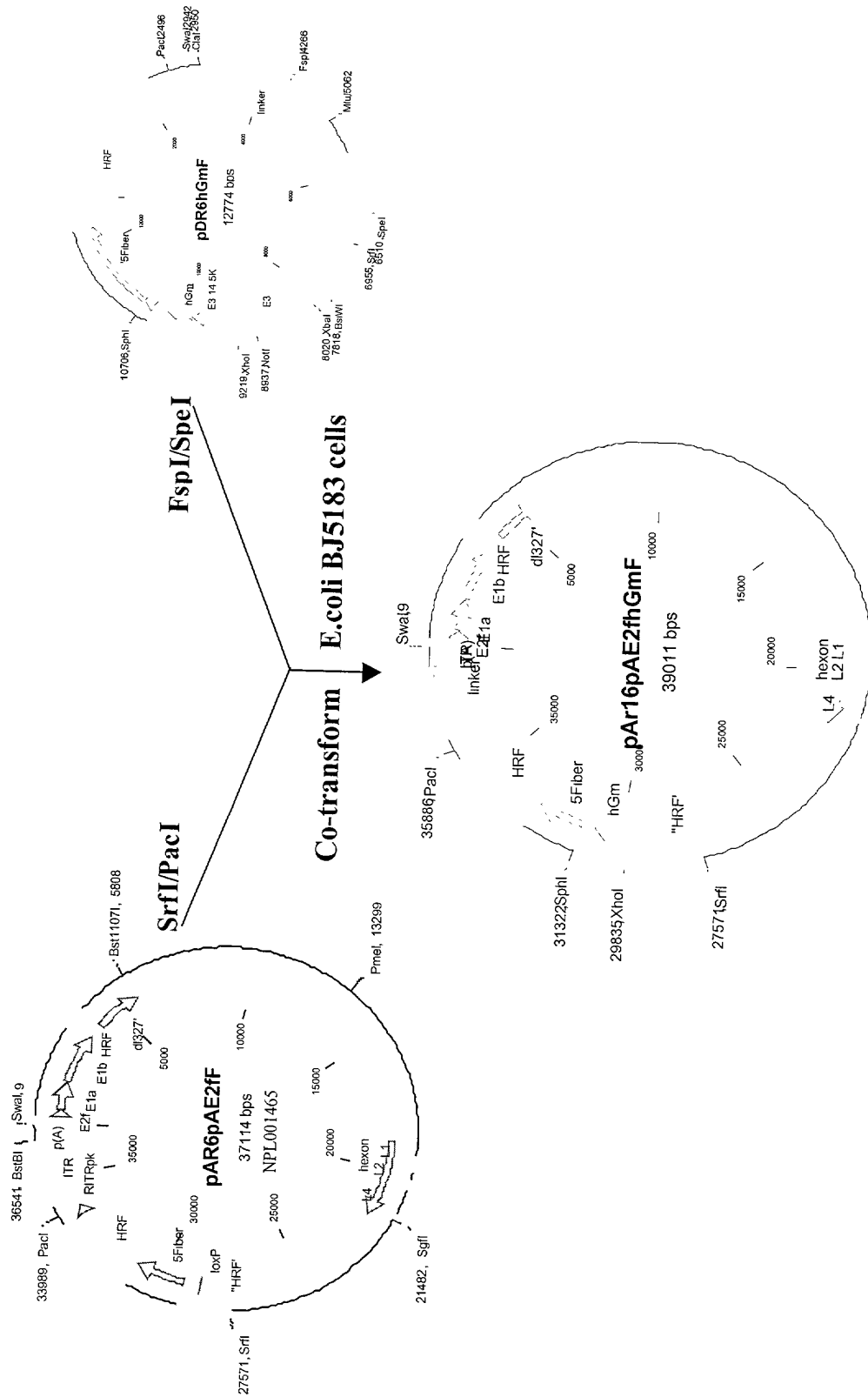


Figure 41. MTS Assay of Δ E3-14.7 hGM-CSF Vector on H460 Tumor Cell Line

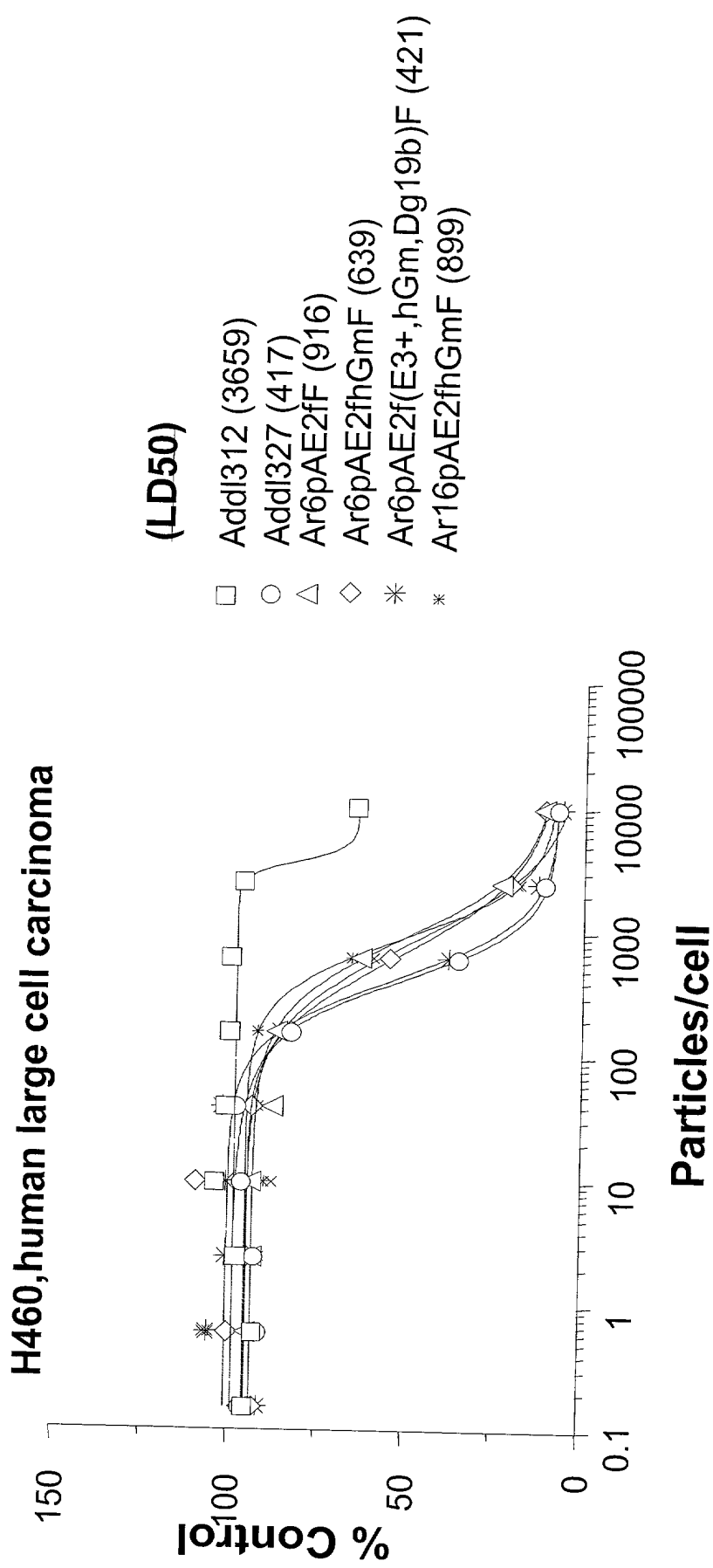
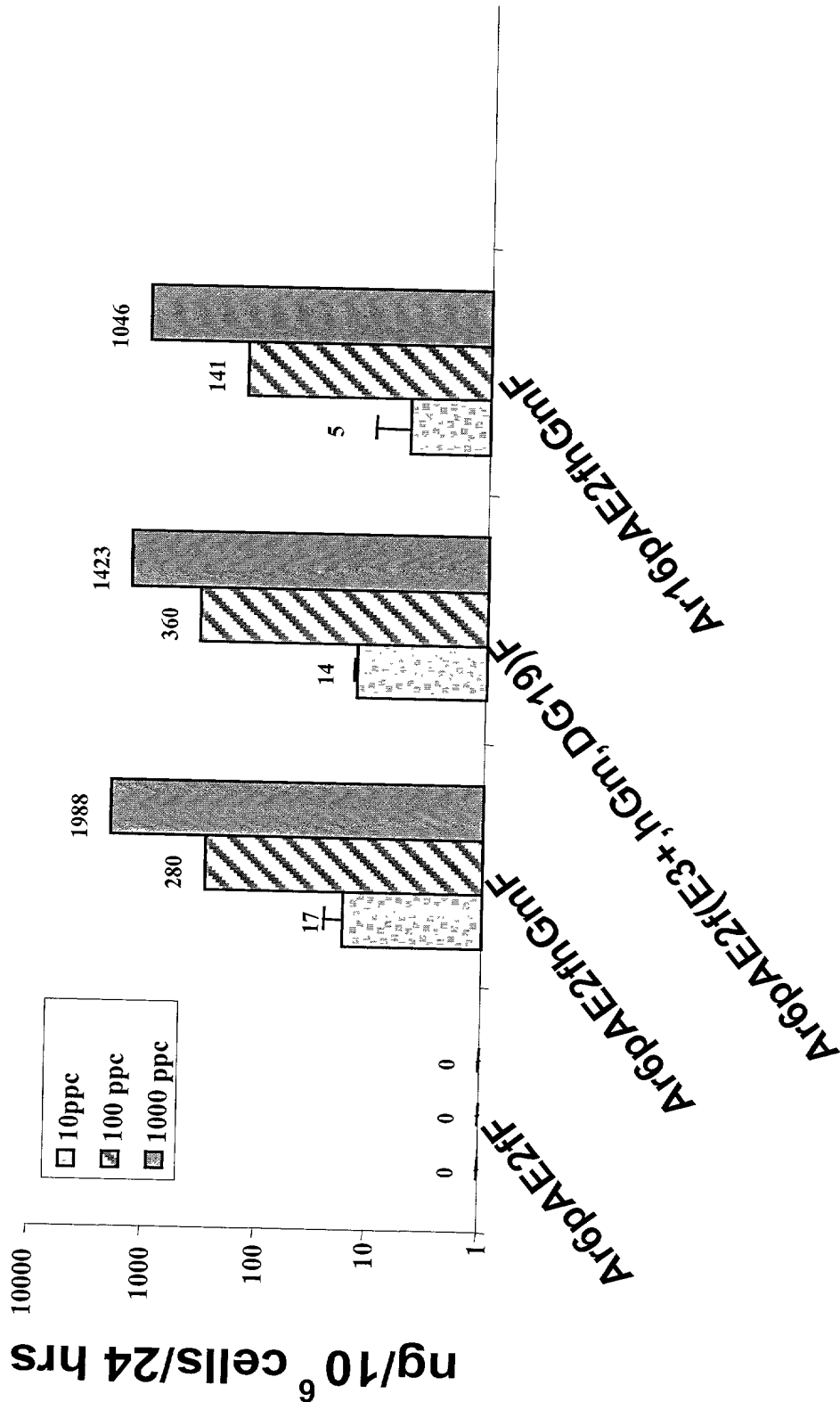
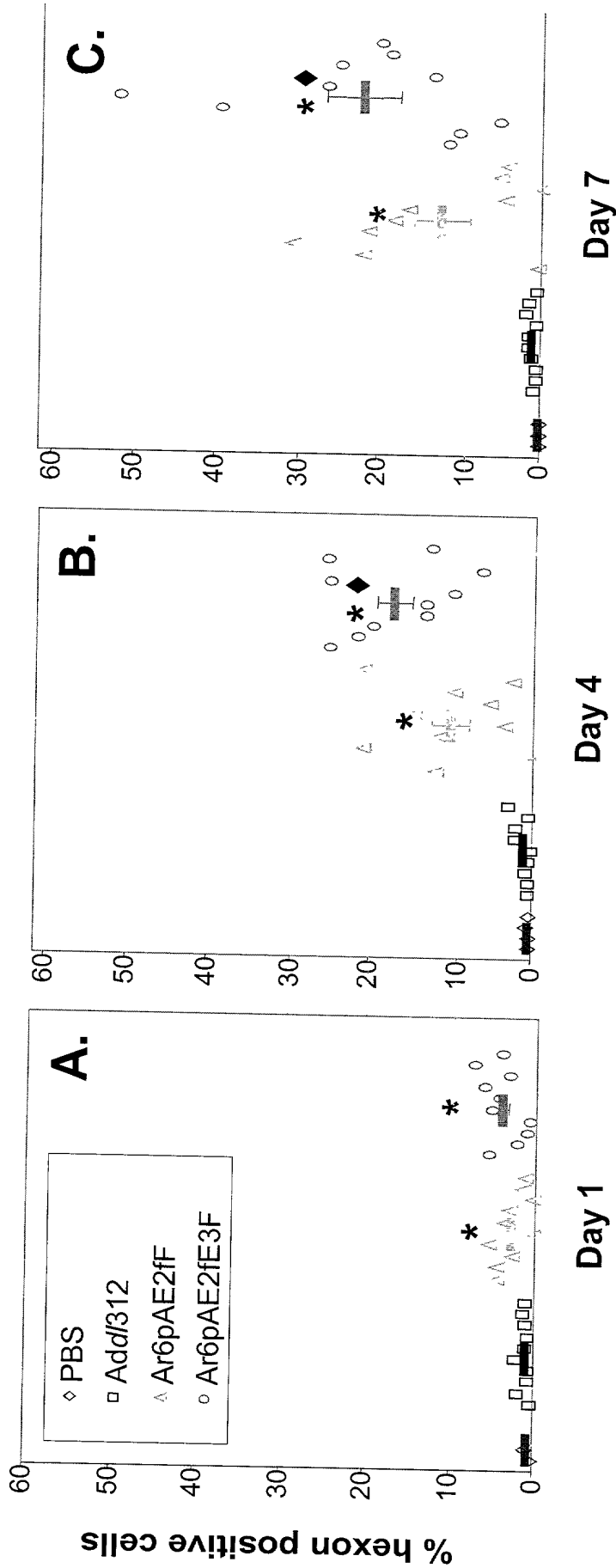


Figure 42. GM-CSF Expression Mediated by Δ E3-14.7 hGM-CSF Vector (Ar16pAE2fhGmF) compared to Ar6pAE2fF, Ar6pAE2fhGmF and Ar6pAE2f(E3+,hGm,Dg19)F in Infected H460 Cells 24 Hours Post-Infection



46/73

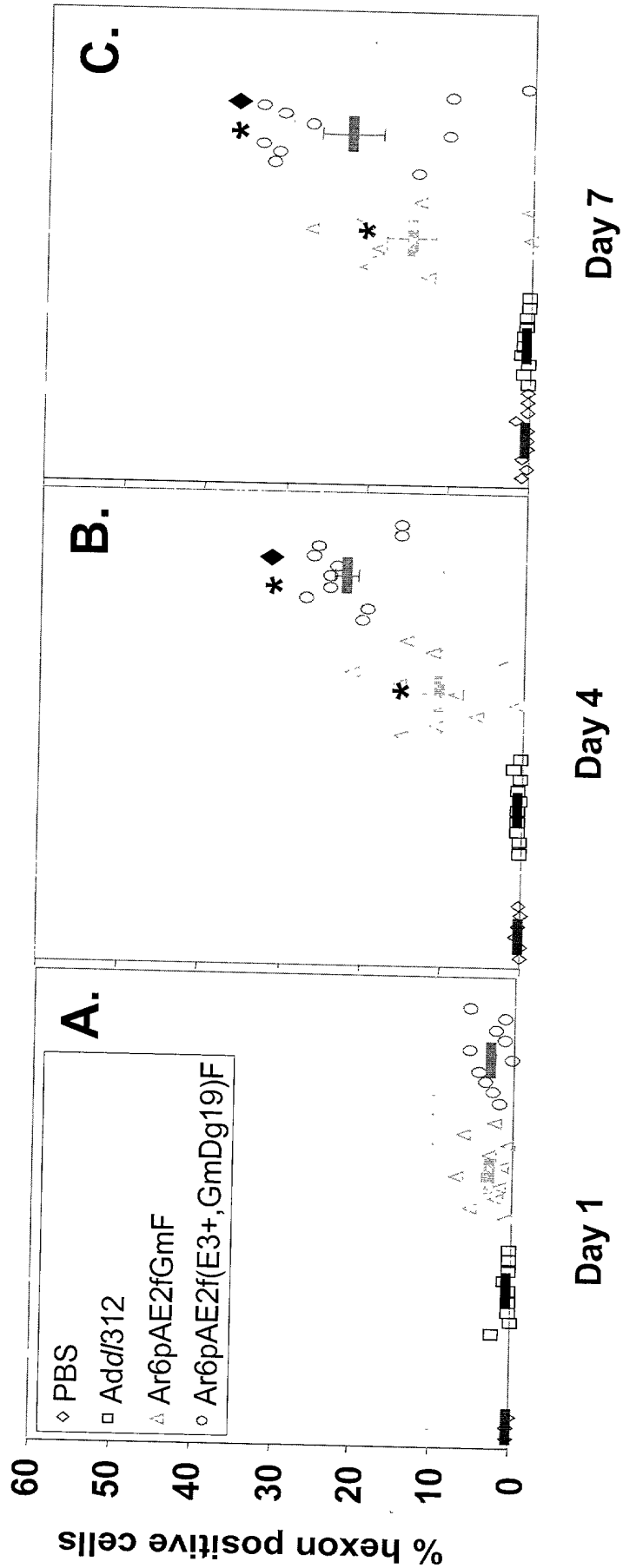
Figure 43. Spread of adenoviruses in H460 xenograft tumors detected by FACS.



*: $p < 0.05$ between Ar6pAE2fF and Ar6pAE2fE3F and Add/312, ANOVA
 ♦: $p < 0.05$ between Ar6pAE2fF and Ar6pAE2fE3F vectors, ANOVA

47/73

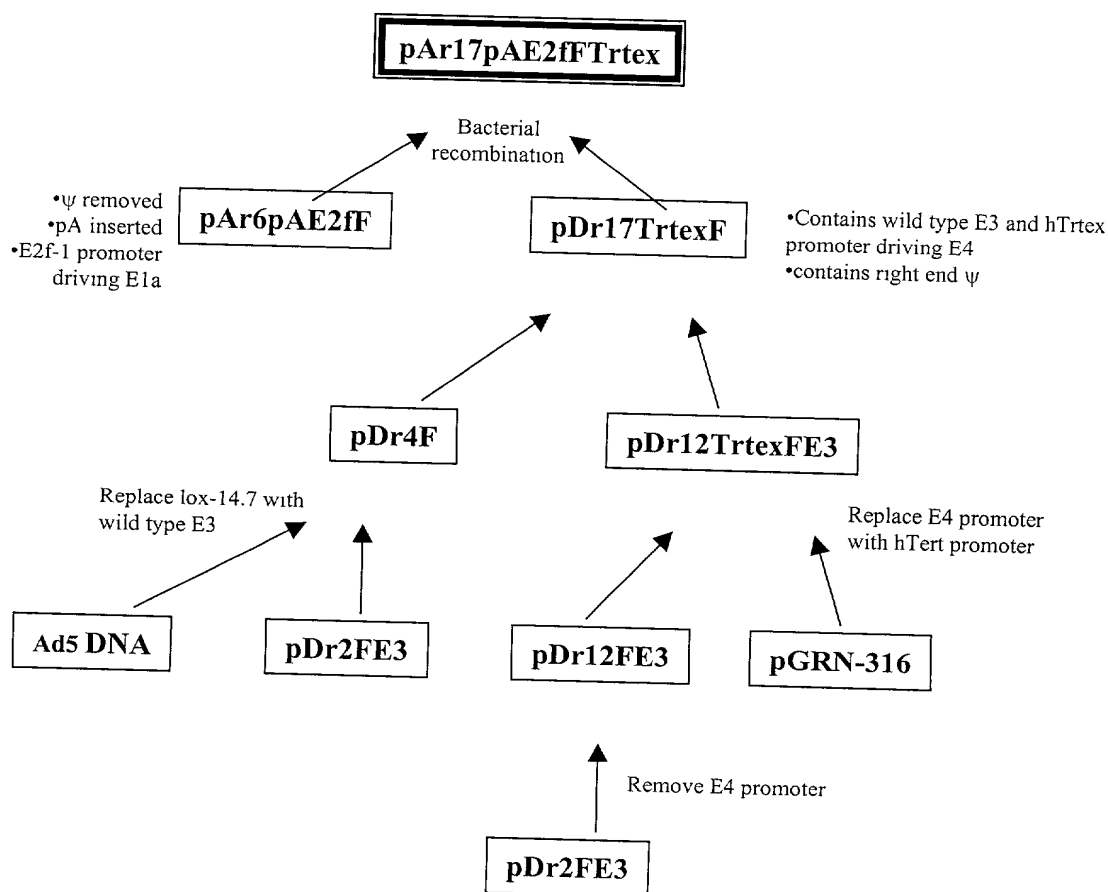
Figure 44. Spread of adenoviruses in Hep3B xenograft tumors detected by FACS.



*: $p < 0.05$ between Ar6pAE2fGmF or Ar6pAE2f(E3+,hGm,Dg19)F and Add/312, ANOVA
*: $p < 0.05$ between Ar6pAE2fGmF and Ar6pAE2f(E3+,hGm,Dg19)F vectors, ANOVA

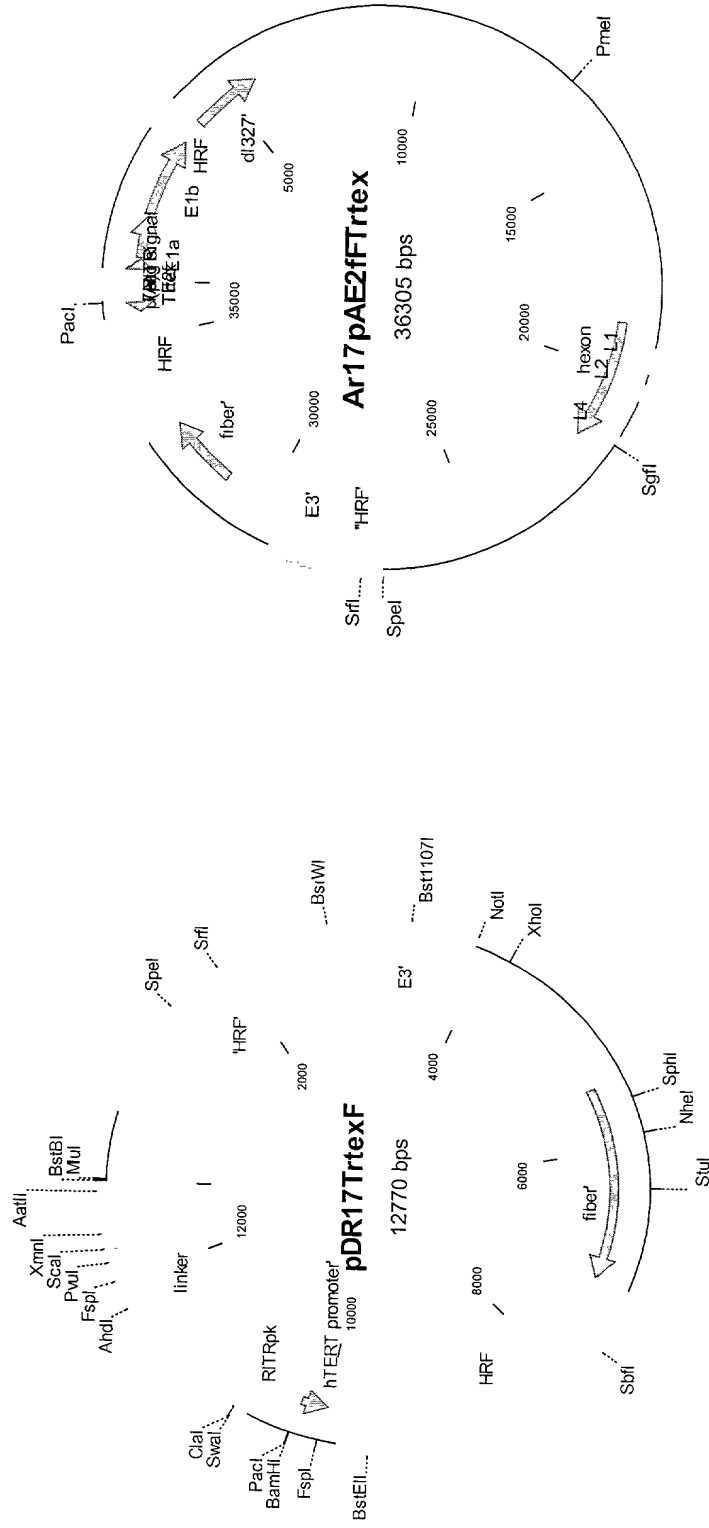
48/73

Figure 45: Flowchart for construction of pAr17pAE2fFTrtex:



1003493 0330

Figure 46: Plasmids used to create oncolytic vector Ar17pAE2fTtrtex



50/73

Figure 47: Sequence of the right end of Ar17pAE2fFTrtex (Seq ID NO:17).

```
35351 agtgctaaaa agcgaccgaa atagcccggg ggaatacata cccgcaggcg
35401 tagagacaac attacagccc ccataggagg tataacaaaa ttaataggag
35451 agaaaaacac ataaacacct gaaaaaccct cctgcctagg caaaatagca
35501 ccctcccgtc ccagaacaac atacagcgct tcacagcggc agcctaacag
35551 tcagccttac cagtaaaaaa gaaaacctat taaaaaaaca cactcggat
35601 caattcgcgg ggggtggccgg ggccaggggc tcccacgtgc gcagcaggac
35651 gcagcgctgc ctgaaactcg cgccgcgagg agagggcggg gccgcggaaa
35701 ggaaggggag gggctgggag ggcccggagg gggctgggcc ggggaccogg
35751 gaggggtcgg gacggggcgg ggtccgcgcg gaggaggcgg agctggaagg
35801 tgaaggggca ggacgggtgc ccgggtcccc agtccctccg ccacgtgggg
35851 ctaggatcct taattaagaa ttctacaatt cccaacacat acaagttact
35901 ccgccctaaa accctgggcg agtctccacg taaacgggtc aagtccccgc
35951 ggccctagac aaatattacg cgctatgagt aacacaaaat tattcagatt
36001 tcacttcctc ttattcagtt ttcccgcgaa aatggccaaa tcttactcgg
36051 ttacgccccaa atttactaca acatccgcct aaaaccgcgc gaaaattgtc
36101 acttcctgtg tacaccggcg cacacaaaa acgtcacttt tgccacatcc
36151 gtcgcttaca tgtgttccgc cactttgca acatcacact tccgccacac
36201 tactacgtca cccgccccgt tcccacgccc cgcgccacgt cacaaactcc
36251 accccctcat tatcatattg gcttcaatcc aaaataaggt atattattga
36301 tgatg
```

1003199.072302

Figure 48: Diagram of Ar17pAE2fTrtex.

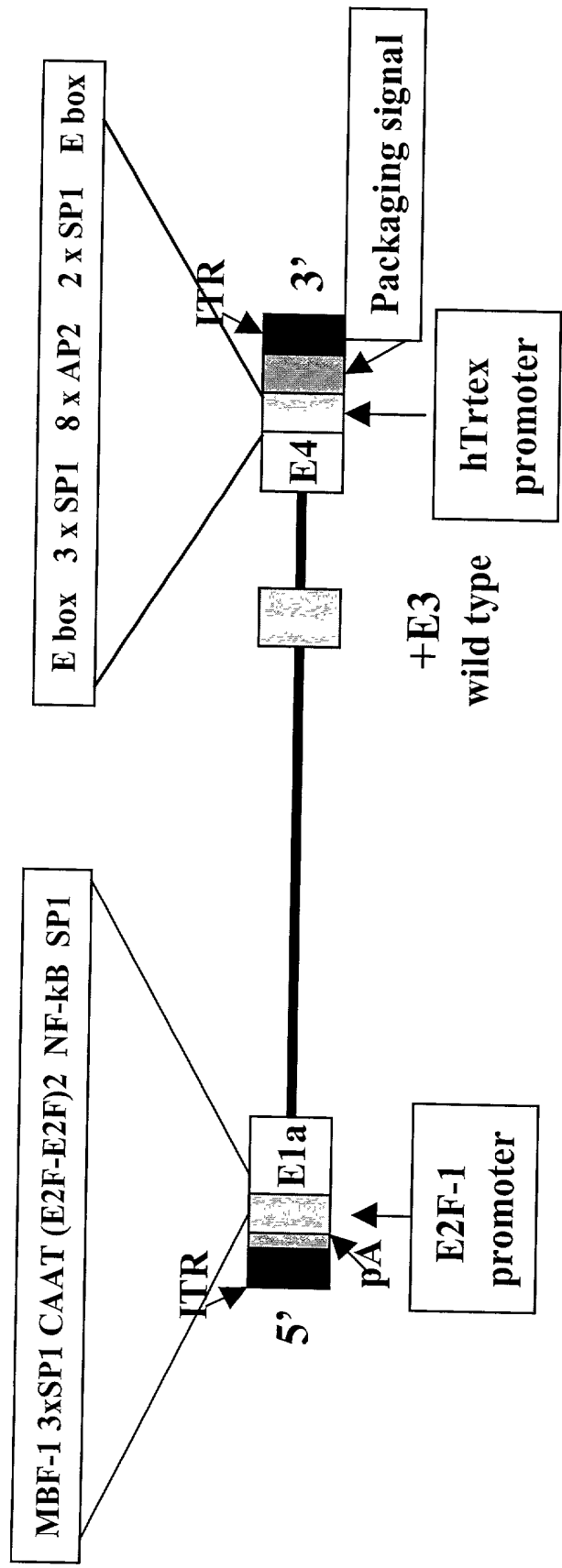


Figure 49. E4 expression is dependent on the hTERT promoter

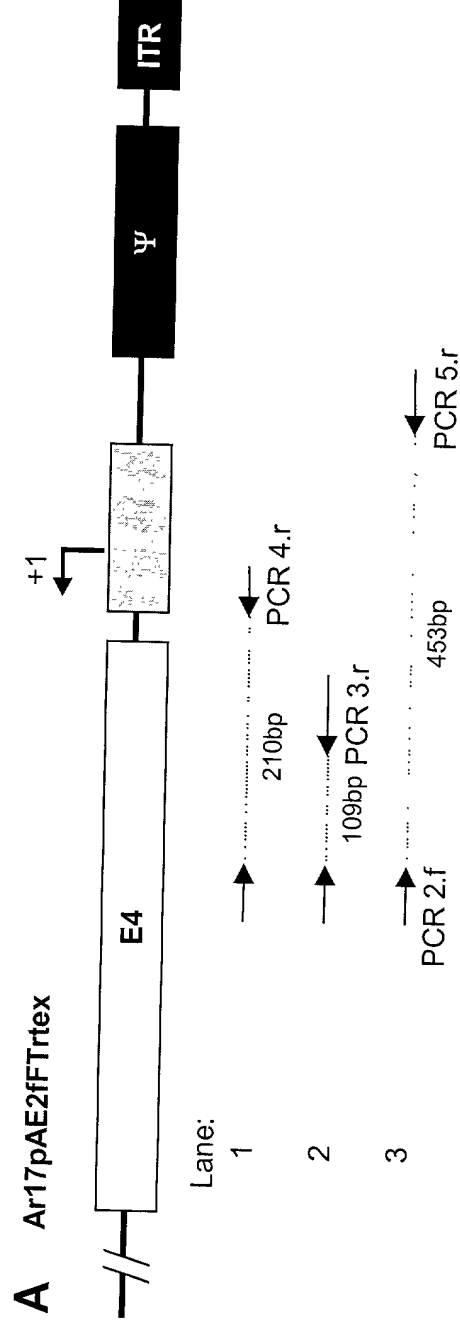
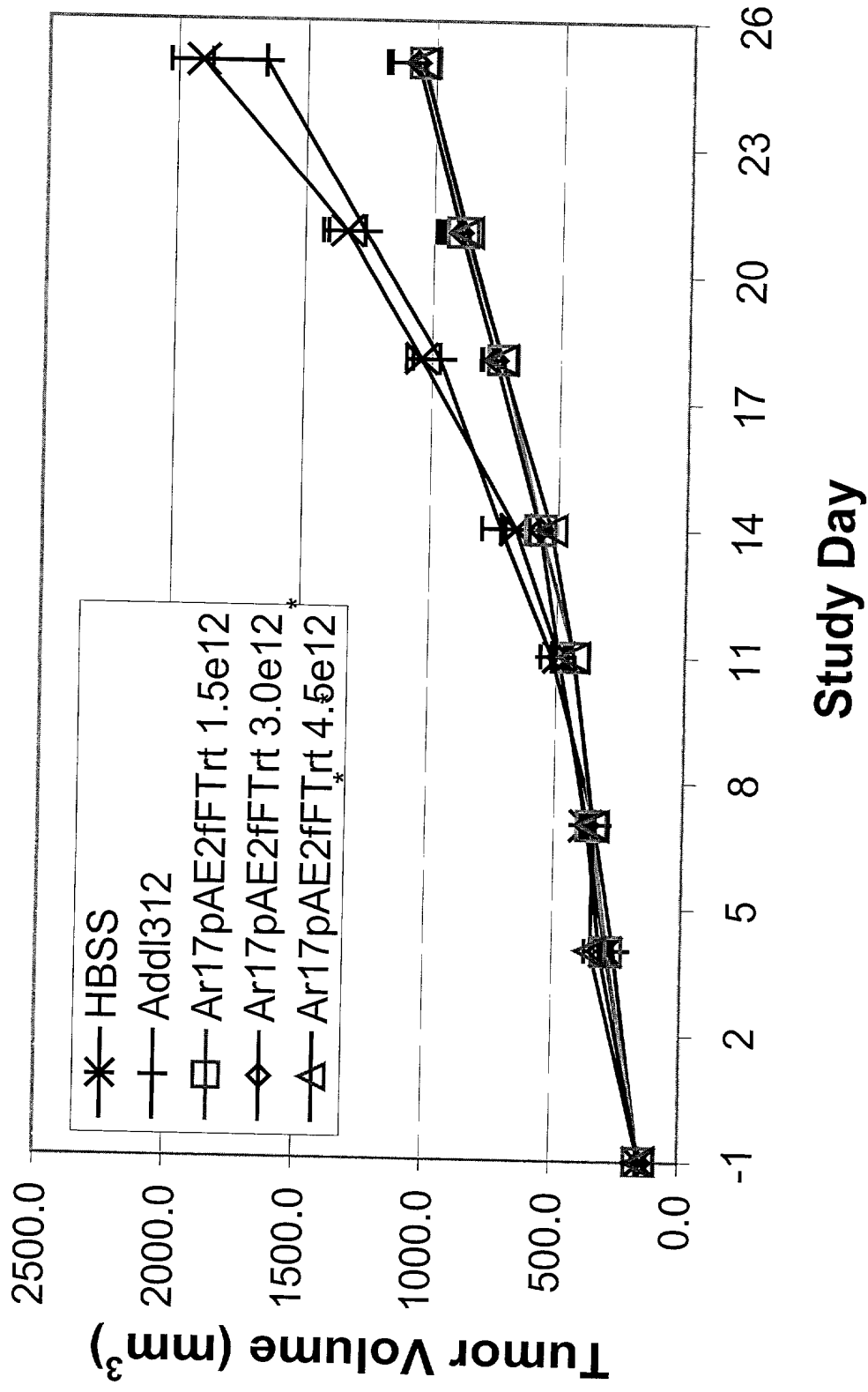


Figure 50. E4 transcription start sites in Ar17pAE2fTrex (Seq ID NO:21)

```
35521 ATACAGCGCT TCACAGCGGC AGCCTAACAG TCAGCCTTAC CAGTAAAAAA GAAAAACCTAT
                               ExtP1
35581 TAAAAAACA CCACTCGGAT CAATTGCGG GGTGGCCGG GGCAGGGCT TCCCACGTGC
                               ←
35641 GCAGCAGGAC GCAGCGCTGC CTGAAACTCG CGCCGCGAGG AGAGGGCGGG GCCGCGGAAA
                               ←
35701 AGGACGGGA CGGGCTGGA TGGCCCGGAA GGGCTGGC CGGGGACCCG GGAAGGGTTC
                               ←
35761 GGCACGGGC GGGTTCCGC GCGGACGAGG CGAGCTGA AGGTGAAGG GCAGGACCGG
                               ←
35821 TGCCCGGTC CCCAGTCCCT CCGCCACGTG GGGCTAGGAT CCTTAATTAA GAATTCTACA
35881 ATTCCCAACA CATACAAGTT ACTCCGCCCT AAAACCCCTG GCG
```

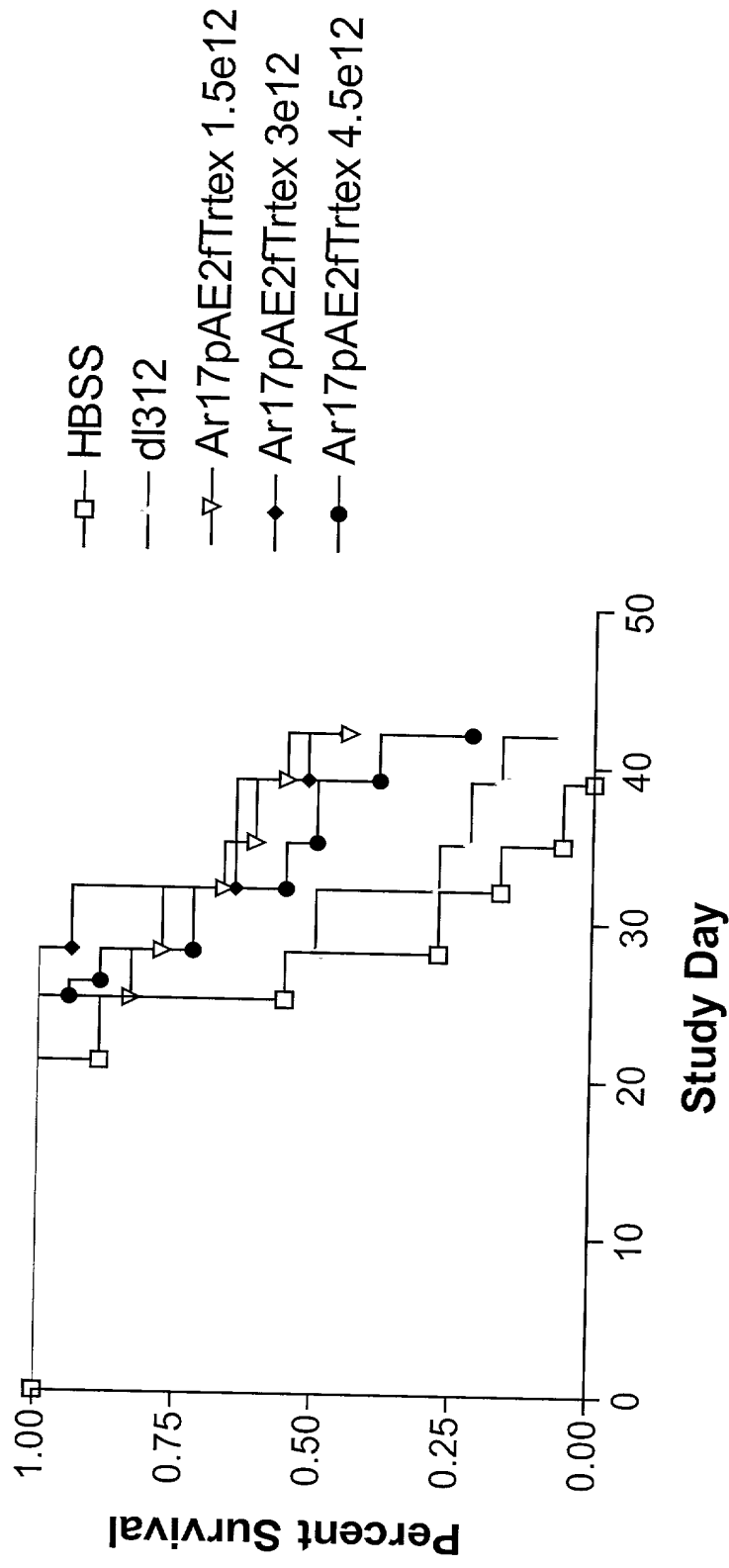
54/73

Figure 51. Efficacy of Ar17pAE2fTrex in Hep3B model.



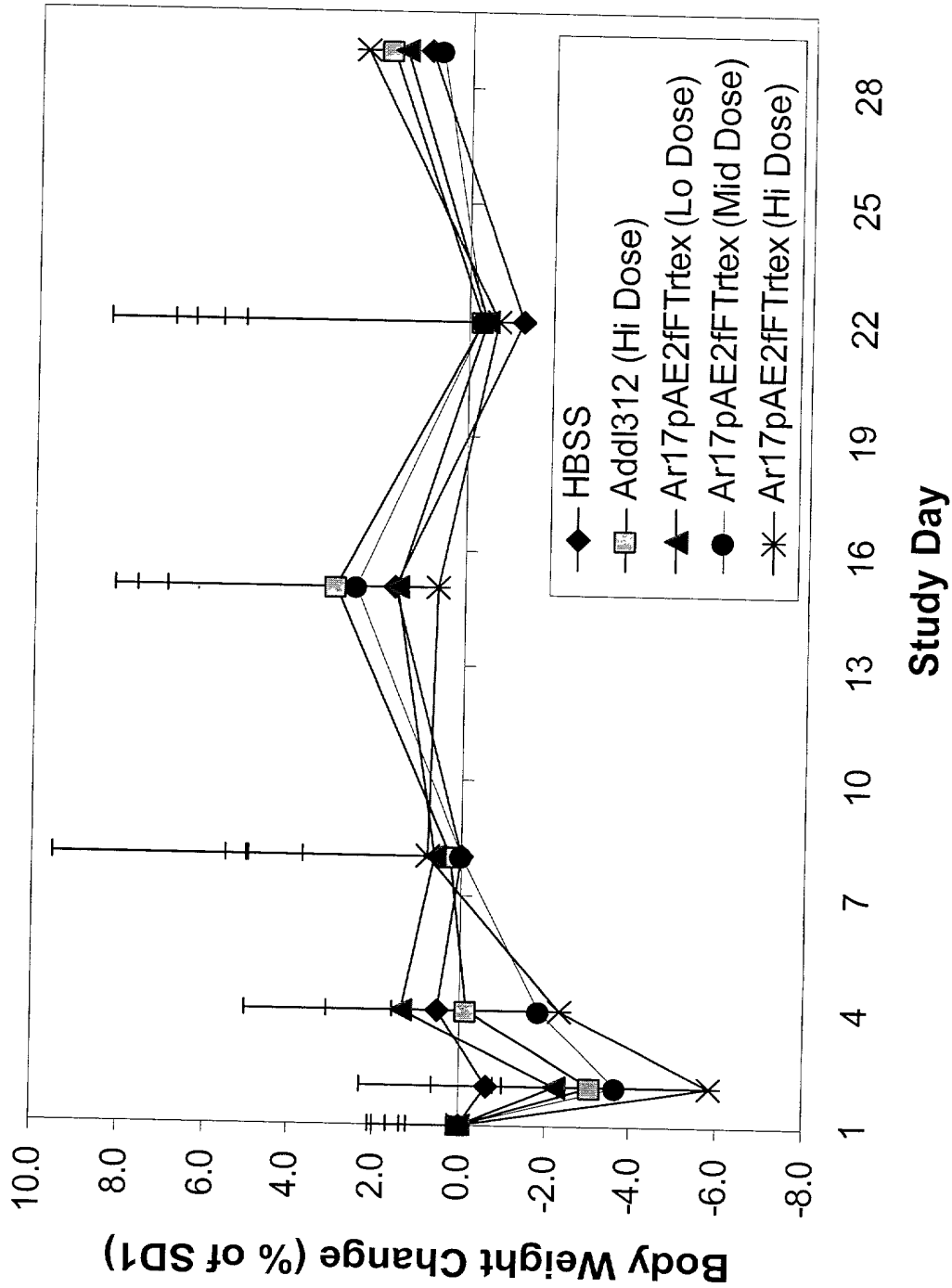
55/73

Figure 52. Effect of Ar17pAE2fTrtex on survival.



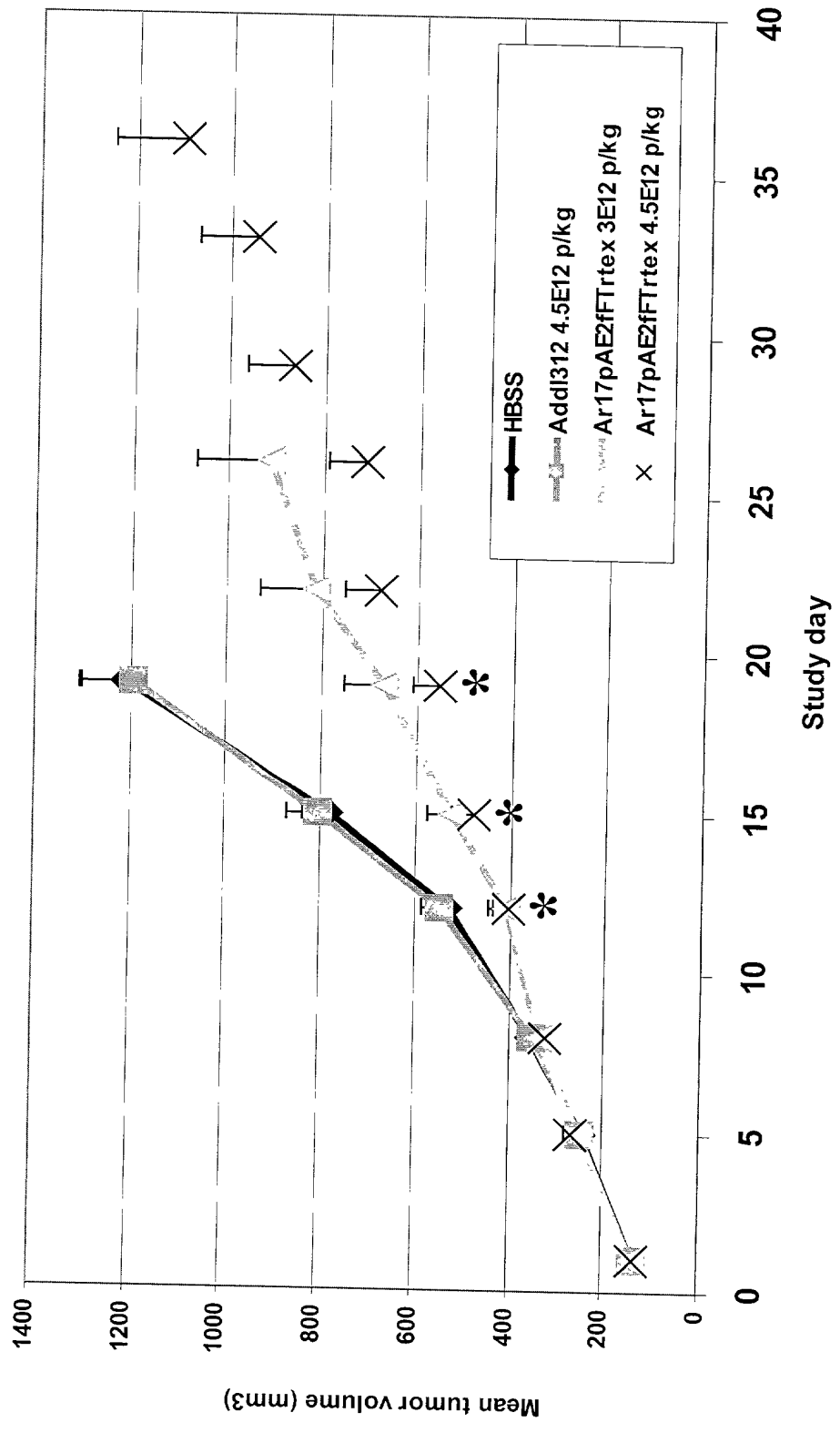
56/73

Figure 53. Body weight changes



57/73

Figure 54. Efficacy of Ar17pAE2fTrtex in Hep3B model.



58/73

Figure 55. Effect of Ar17pAE2fTrtex on survival.

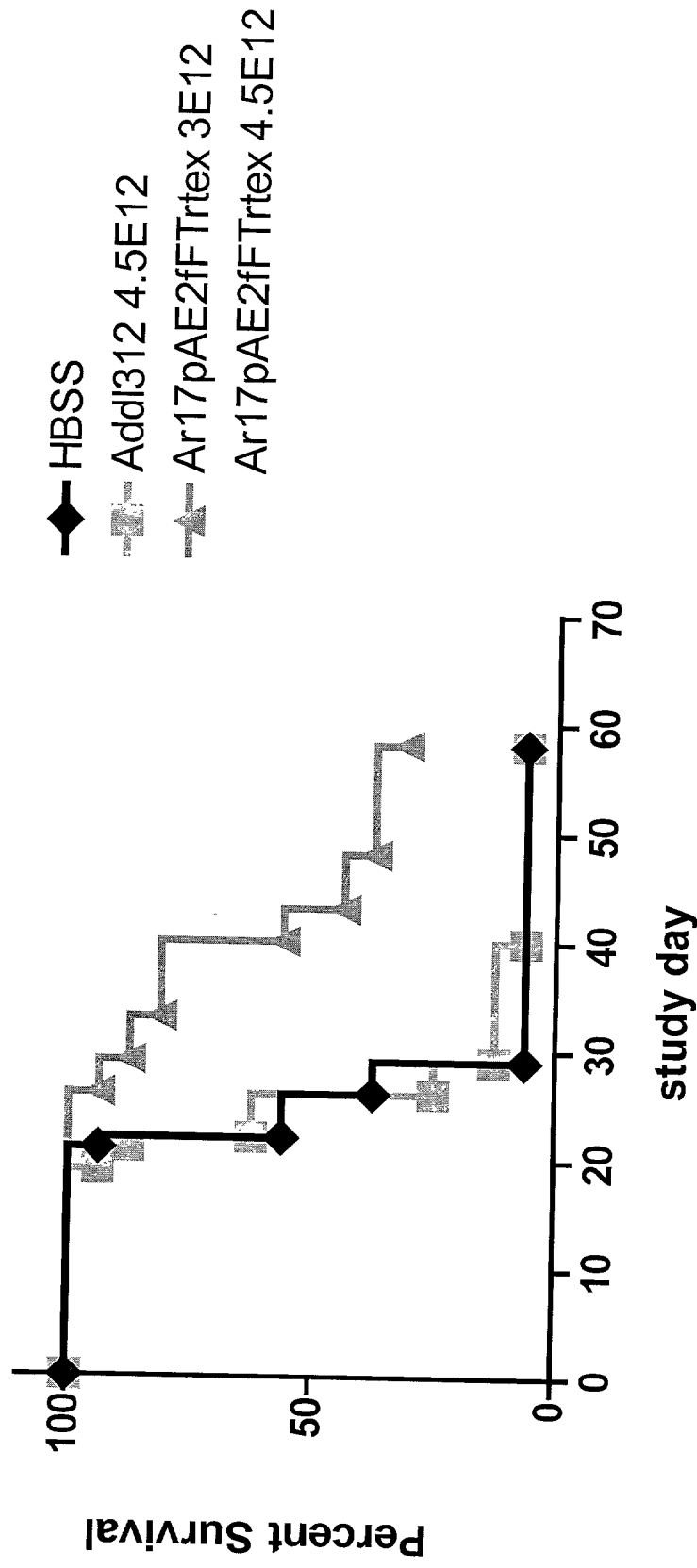
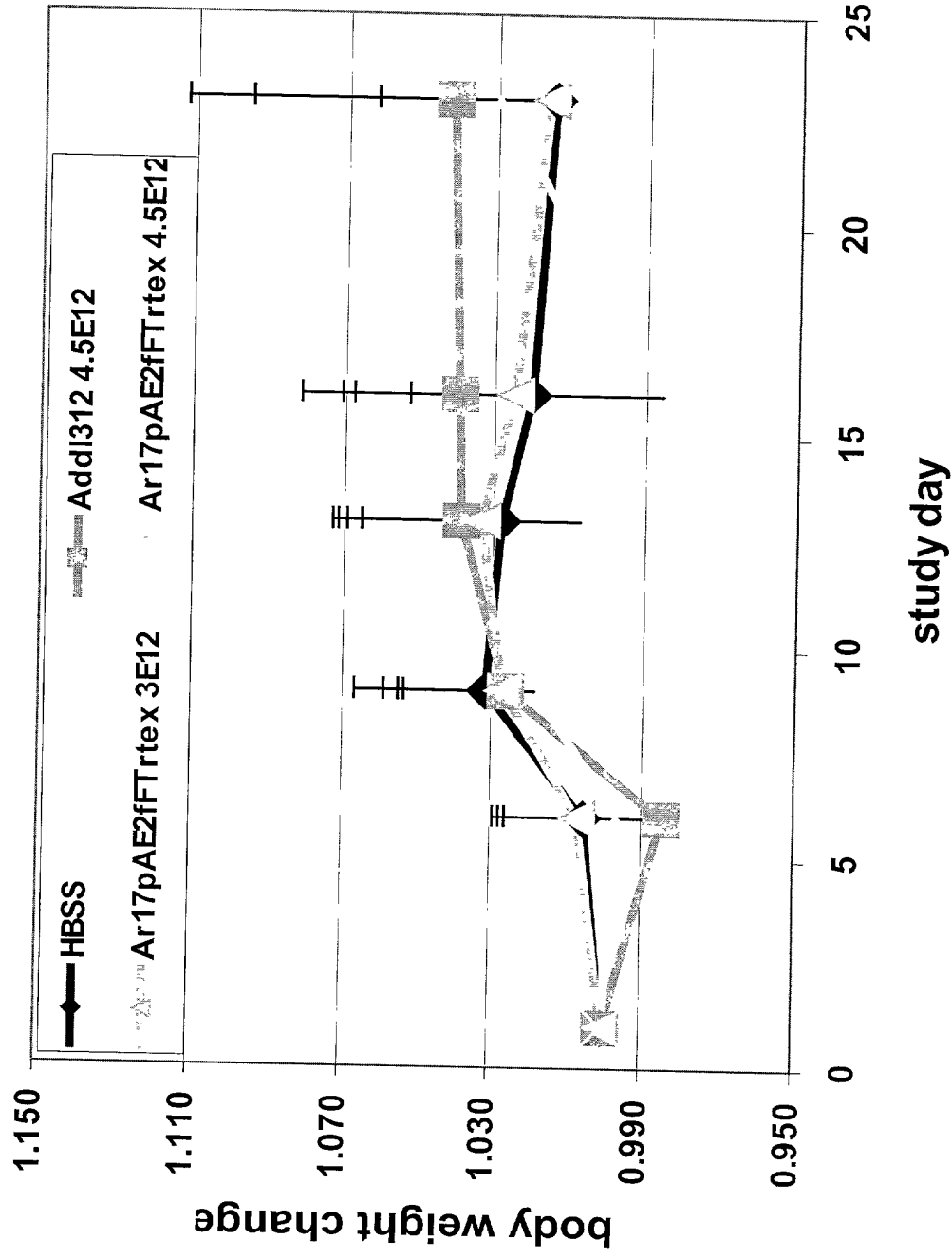
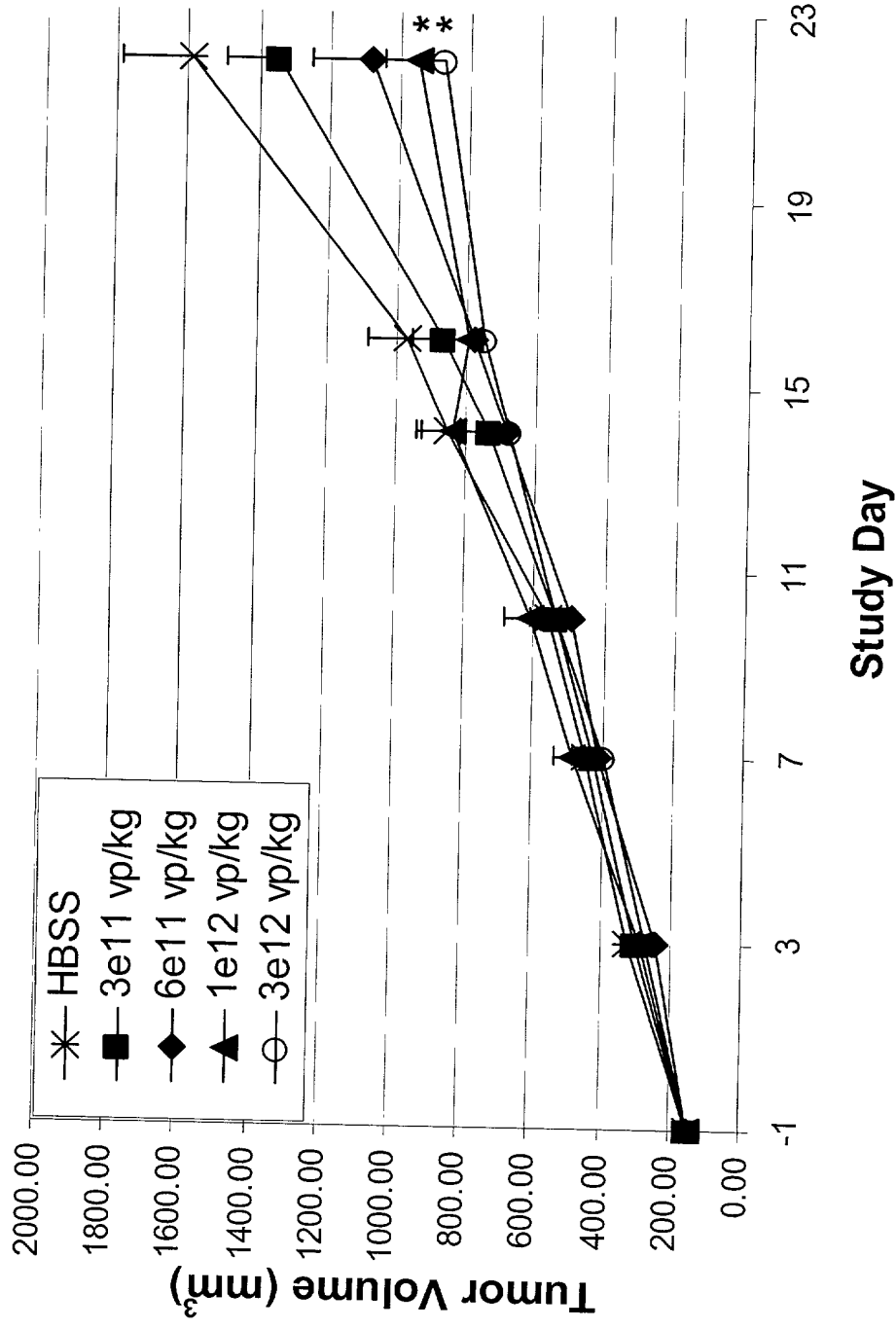


Figure 56. Body weight changes



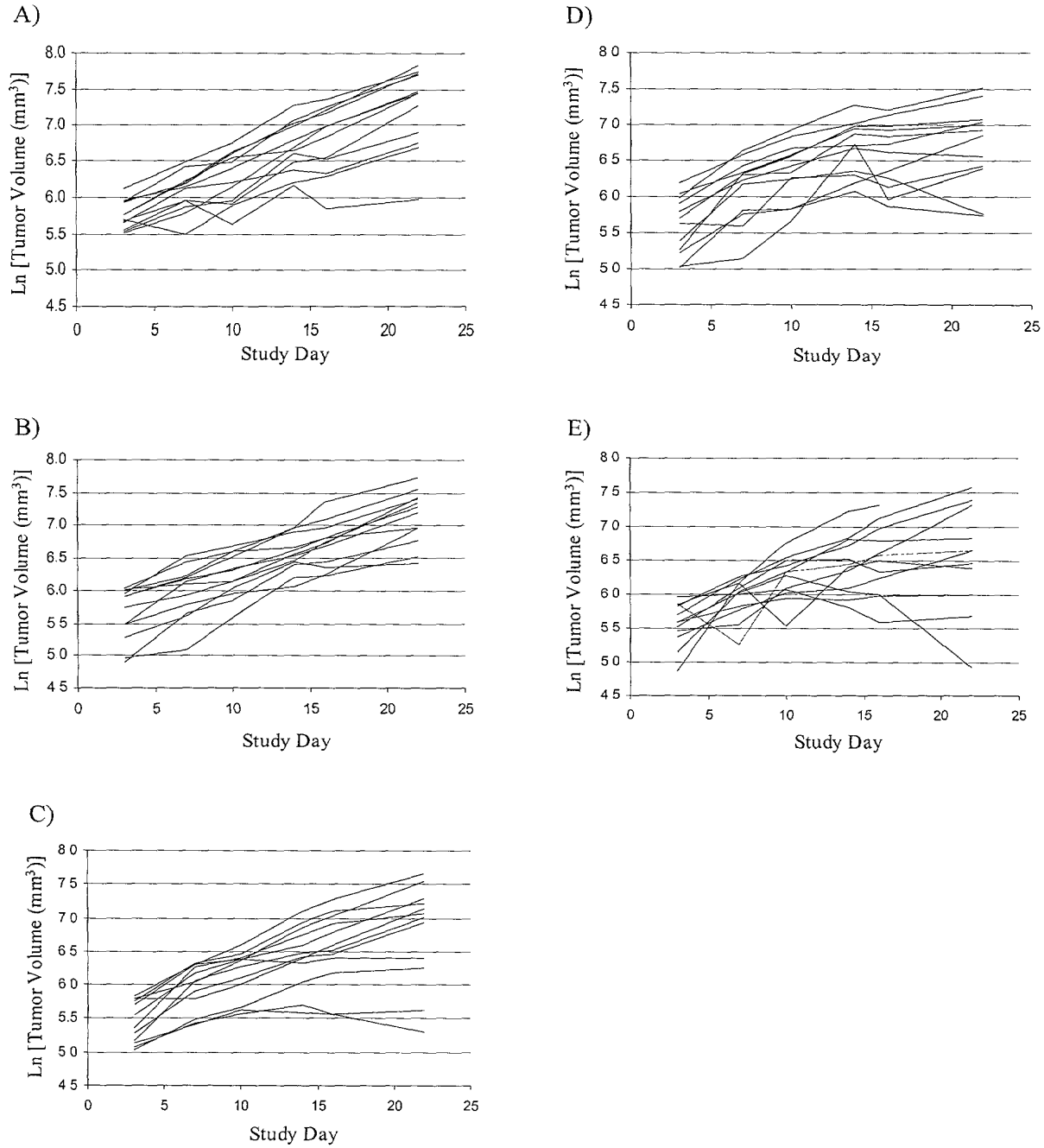
60/73

Figure 57 Dose-dependent anti-tumor efficacy



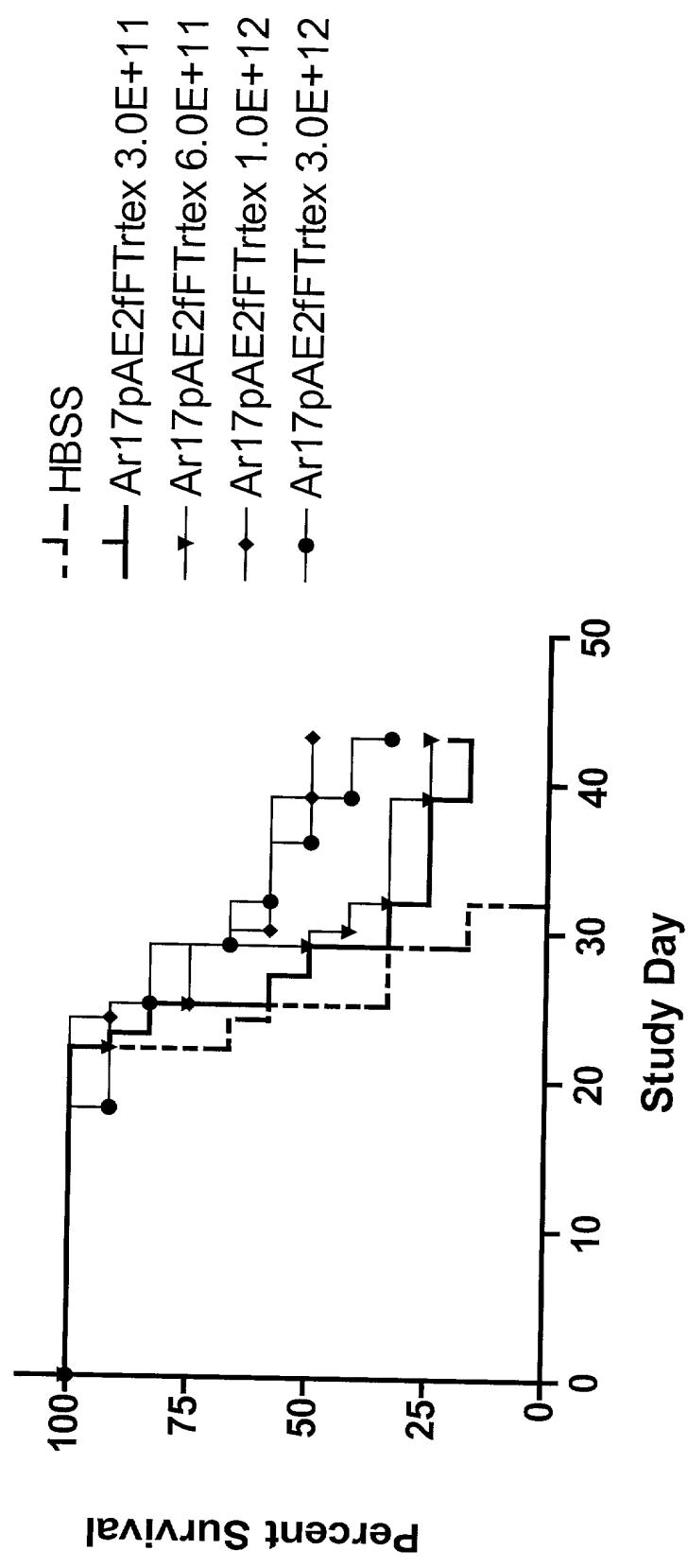
61/73

Figure 58. Individual tumor volumes following intravenous administration of Ar17pAE2fFTrtex



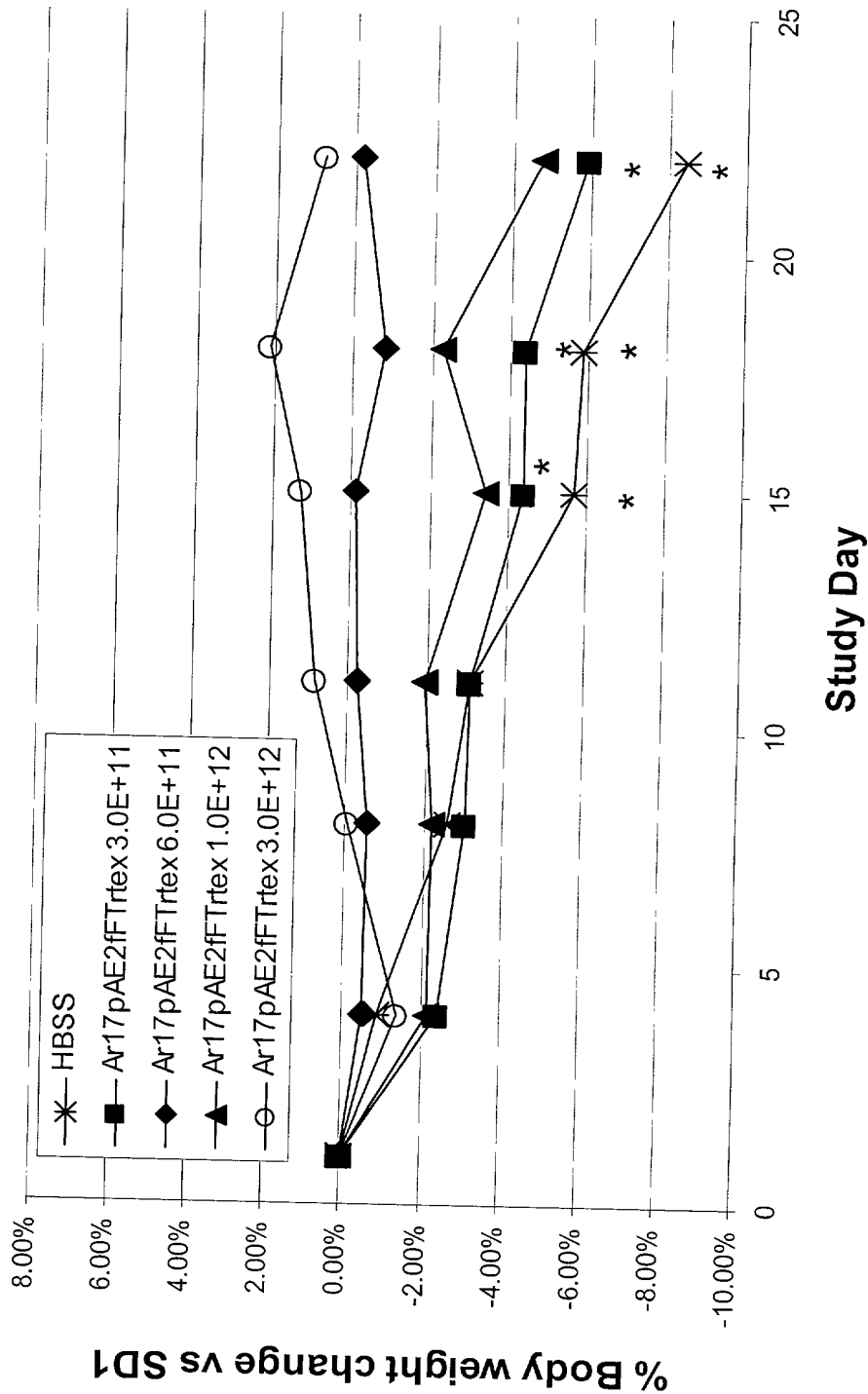
62/73

Figure 59. Effect of Ar17pAE2fTrtex on survival.



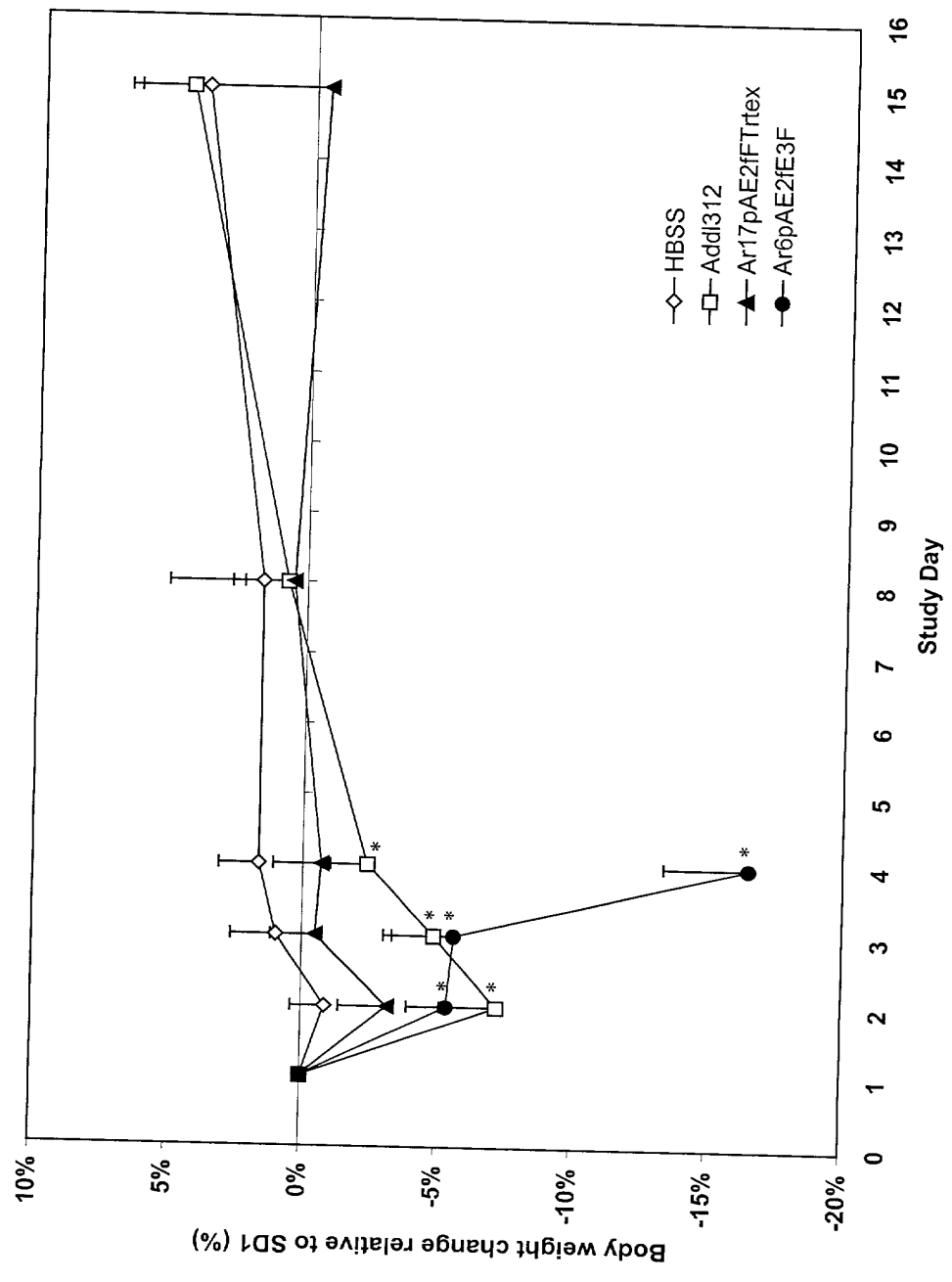
63/73

Figure 60. Body weight (% change)



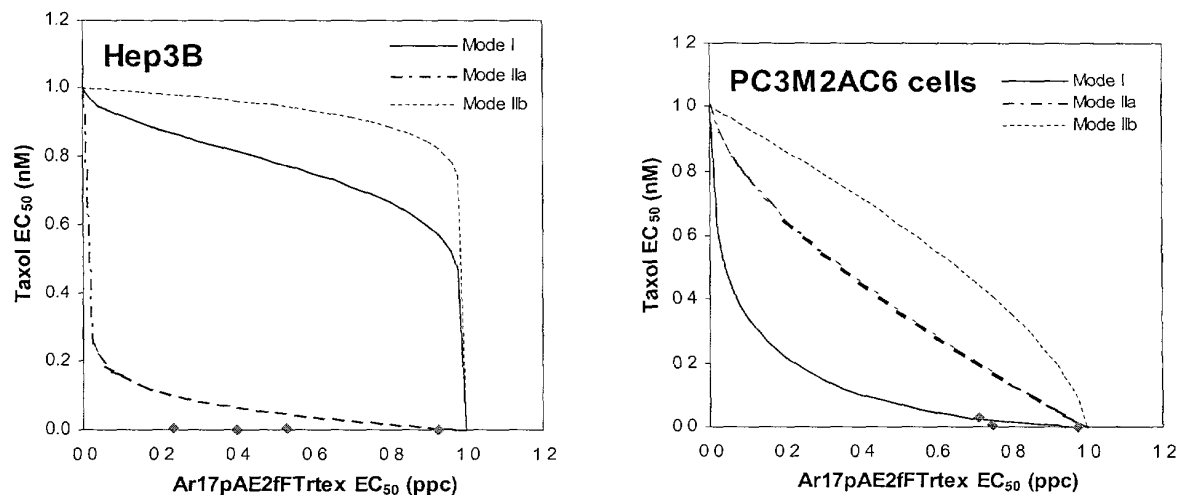
65/73

Figure 62. Effect on body weight in SCID mice



66/73

Figure 63. Improved isobologram with additivity envelope for Ar17pAE2fFTrtex and Taxol against Hep 3B and PC3M.2AC6 cells.

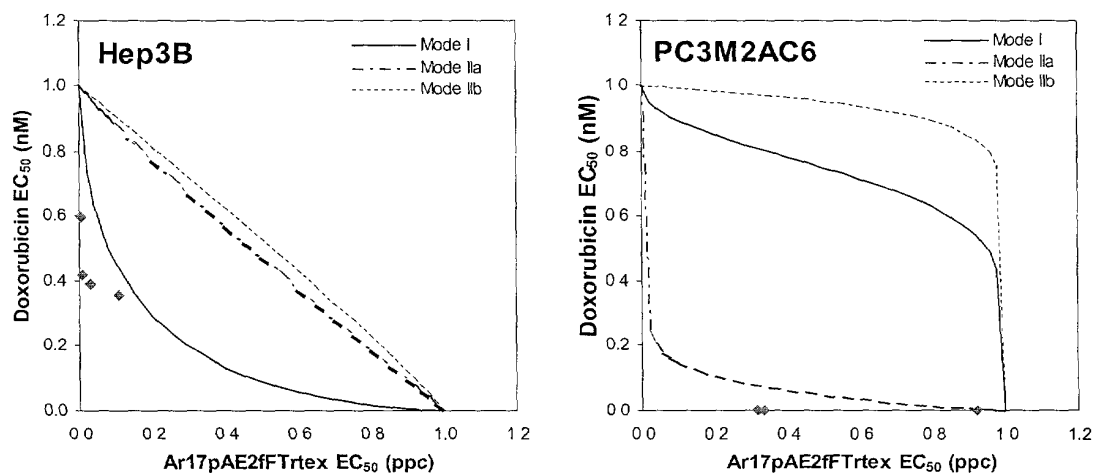


MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
8.3e-05	0.23	0.0043	synergy
3.3e-04	0.53	0.0024	synergy
1.3e-03	0.40	0.00046	synergy
5.3e-03	0.93	0.00027	synergy

MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
0.02	3.4	1.3	antagonism
0.2	0.71	0.028	synergy
2	0.75	0.003	synergy
20	0.97	0.0004	synergy

67/73

Figure 64. Improved isobologram with additivity envelope for Ar17pAE2fFTrtex and Doxorubicin against Hep 3B and PC3M.2AC6 cells.

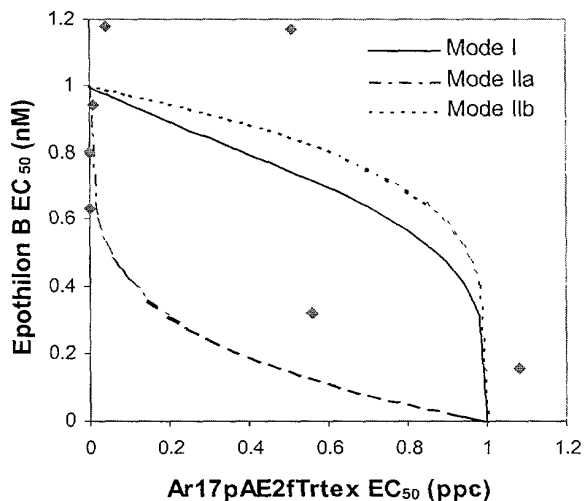


MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
1.3e-05	0.0028	0.60	synergy
5.0e-05	0.0078	0.42	synergy
2.0e-04	0.029	0.39	synergy
8.0e-04	0.11	0.36	synergy

MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
1	2.2	0.015	antagonism
10	0.92	6.1e-4	synergy
100	0.34	2.2e-5	synergy
1000	0.32	2.1e-6	synergy

68/73

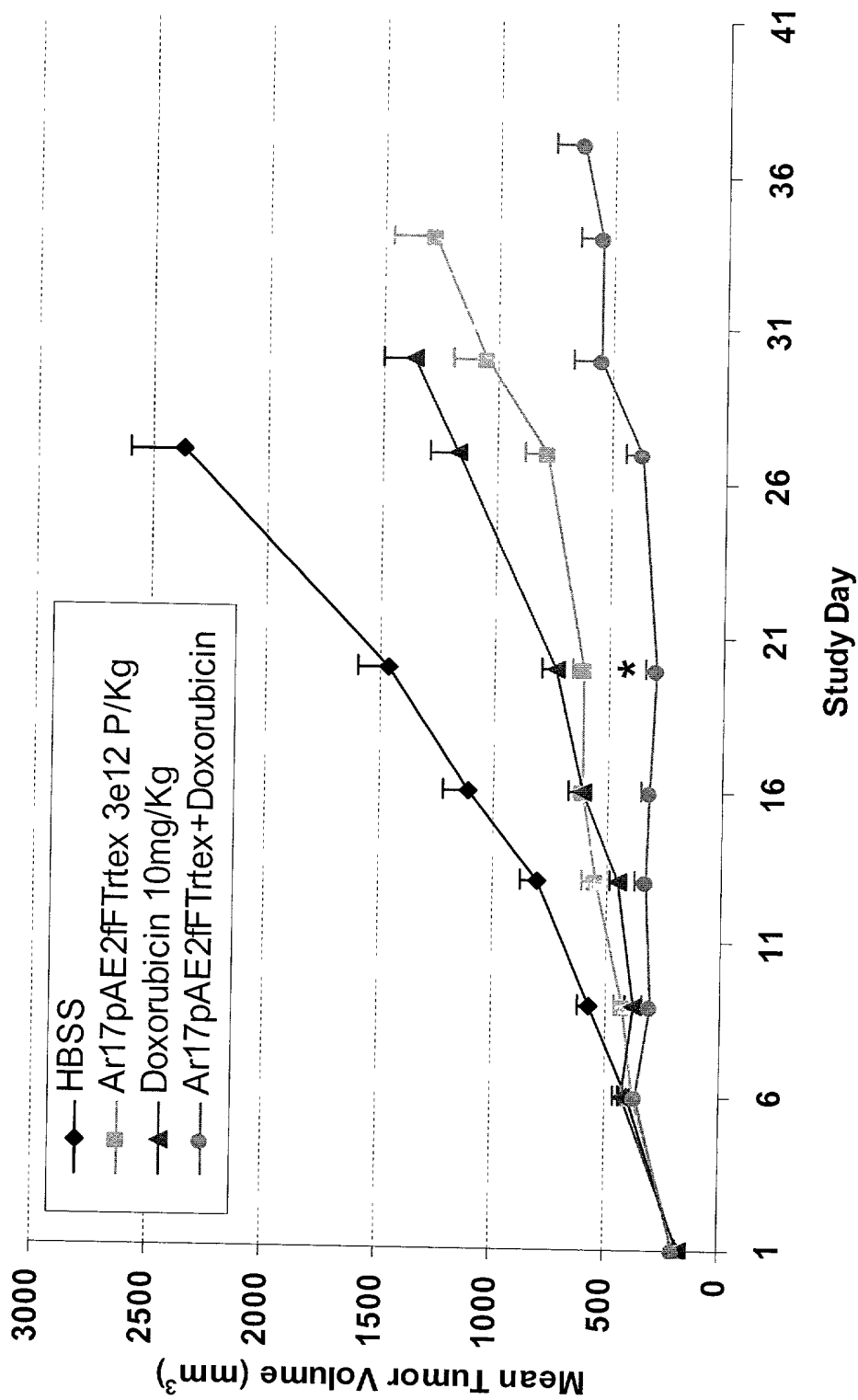
Figure 65. Improved isobologram with additivity envelope for Ar17pAE2fTrtex and Epothilone B against Hep 3B cells.



	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
3.1e-06	0.00045	0.63	synergy
1.3e-05	0.0018	0.80	synergy
5.0e-05	0.0084	0.95	synergy
2.0e-04	0.042	1.2	antagonism
8.0e-04	0.18	1.6	antagonism
3.2e-03	0.51	1.2	antagonism
1.3e-02	0.56	0.32	additivity
5.1e-02	1.1	0.06	antagonism

69/73

Figure 66. Doxorubicin Combination: Mean Tumor Volumes



70/73

Figure 67. Doxil® Combination Mean Tumor Volumes

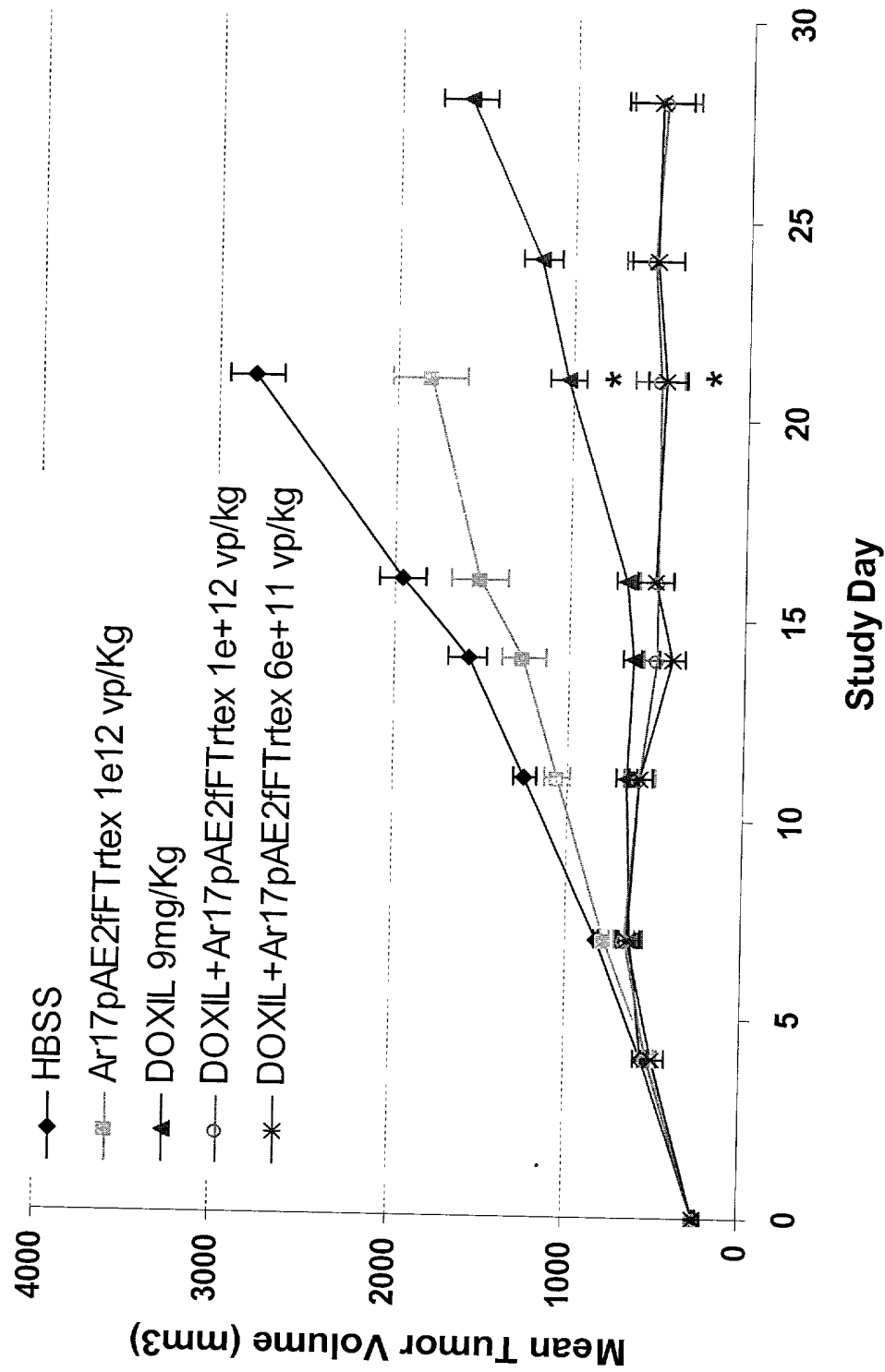


Figure 68. Cytotoxicity assessed in primary human hepatocytes

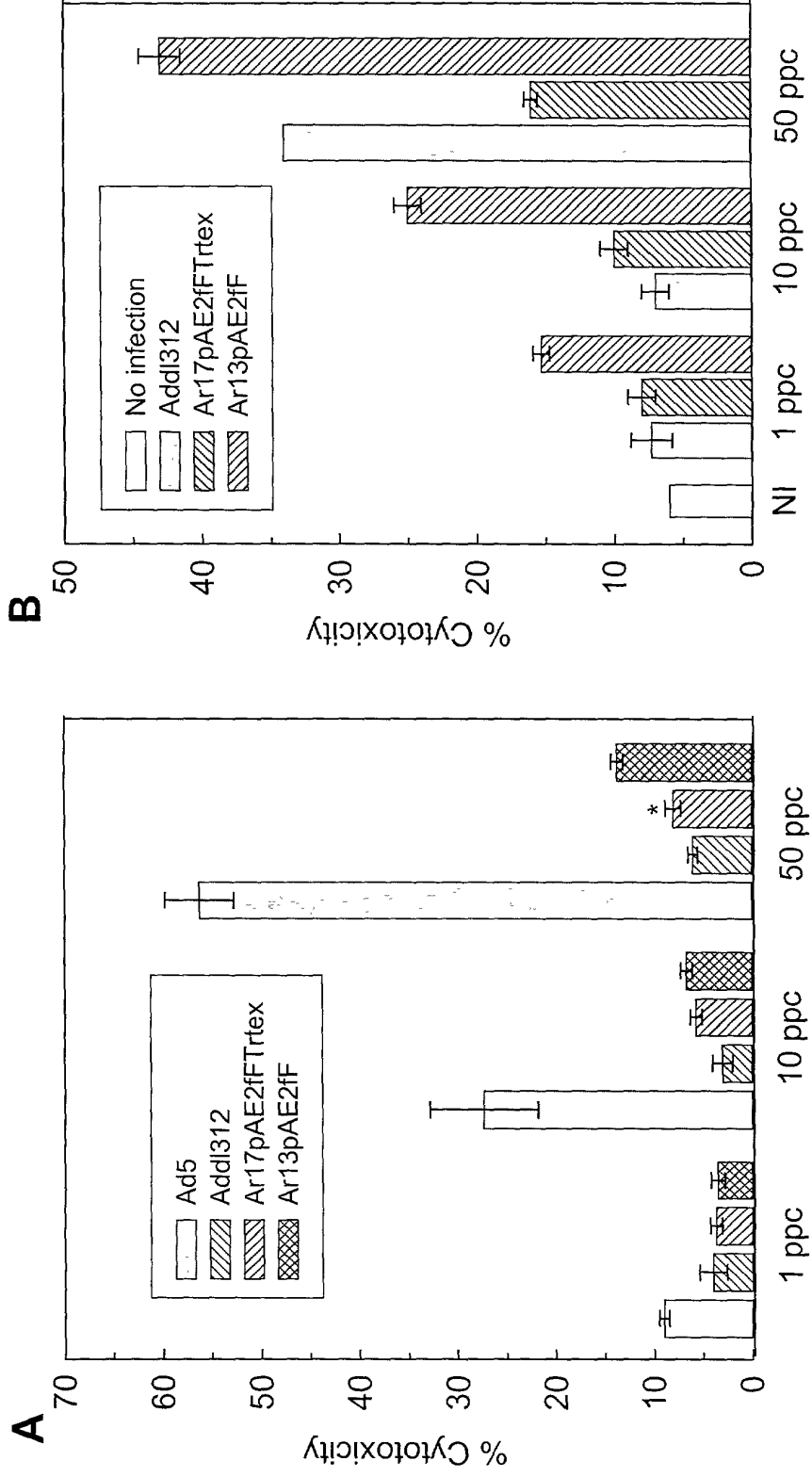
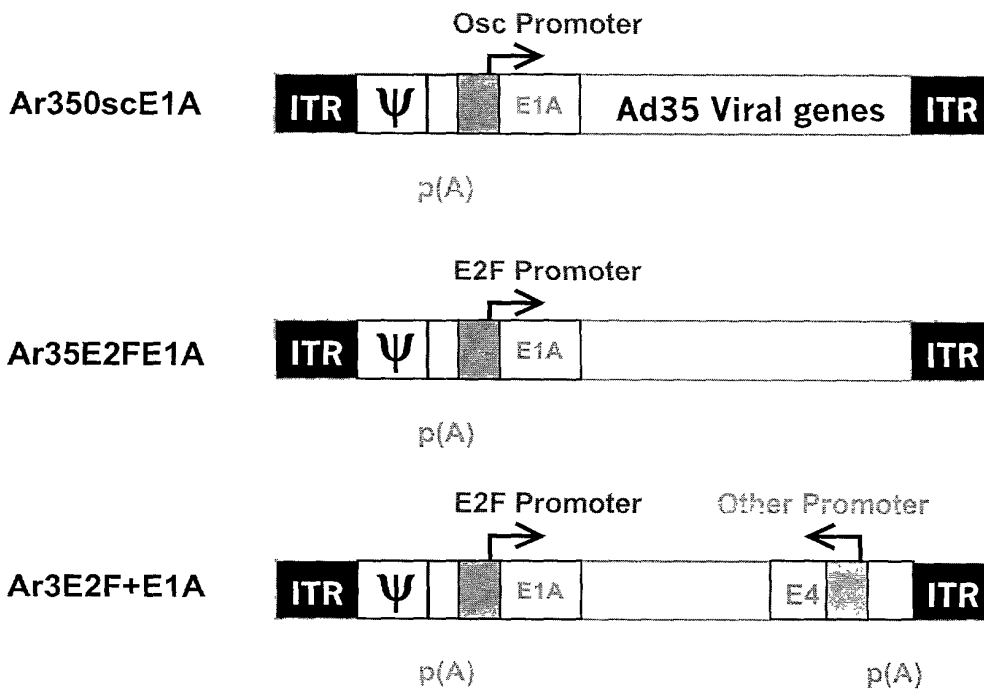


Figure 69

Ad35-Based Oncolytic Vectors



73/73

Figure 70

